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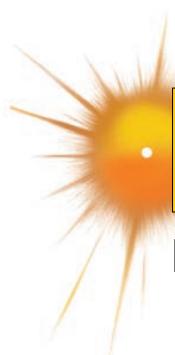
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Section 1 Diagnosis of Respiratory Disorders

284 Approach to the Patient with Disease of the Respiratory System

Bruce D. Levy



The majority of diseases of the respiratory system present with cough and/or dyspnea and fall into one of three major categories: (1) obstructive; (2) restrictive; and (3) vascular diseases. Obstructive pathophysiology is most common and primarily results from airway diseases, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis. Diseases resulting in restrictive pathophysiology include parenchymal lung diseases, abnormalities of the chest wall and pleura, and neuromuscular disease. Pulmonary embolism, pulmonary hypertension, and pulmonary venoocclusive disease are examples of disorders of the pulmonary vasculature. Although many specific diseases fall into these major categories, both infective and neoplastic processes can affect the respiratory system and result in myriad pathologic findings, including those listed in the three categories above (**Table 284-1**).

Disorders can also be grouped according to gas exchange abnormalities, including hypoxemia, hypercarbia, or combined impairment; however, many respiratory disorders do not manifest as gas exchange abnormalities.

As with the evaluation of most patients, the approach to a patient with a respiratory system disorder begins with a thorough history

TABLE 284-1 Categories of Respiratory Disease

CATEGORY	EXAMPLES
Obstructive pathophysiology—airway disease	Asthma Chronic obstructive pulmonary disease (COPD) Bronchiectasis Bronchiolitis
Restrictive pathophysiology—parenchymal disease	Idiopathic pulmonary fibrosis (IPF) Asbestosis Desquamative interstitial pneumonitis (DIP) Sarcoidosis
Restrictive pathophysiology—neuromuscular weakness	Amyotrophic lateral sclerosis (ALS) Guillain-Barré syndrome Myasthenia gravis
Restrictive pathophysiology—chest wall/pleural disease	Kyphoscoliosis Ankylosing spondylitis Chronic pleural effusions
Pulmonary vascular disease	Pulmonary embolism Pulmonary arterial hypertension (PAH) Pulmonary venoocclusive disease Vasculitis
Malignancy	Bronchogenic carcinoma (non-small-cell and small-cell lung cancer) Metastatic disease
Infectious diseases	Pneumonia Bronchitis Tracheitis

and a focused physical examination. Many patients will subsequently undergo pulmonary function testing, chest imaging, blood and sputum analysis, a variety of serologic or microbiologic studies, and diagnostic procedures, such as bronchoscopy. This stepwise approach is discussed in detail below.

HISTORY

Dyspnea and Cough The cardinal symptoms of respiratory disease are dyspnea and cough (**Chaps. 37 and 38**). Dyspnea has many causes, some of which are not predominantly due to lung pathology. The words a patient uses to describe shortness of breath can suggest certain etiologies for dyspnea. Patients with obstructive lung disease often complain of “chest tightness” or “inability to get a deep breath,” whereas patients with congestive heart failure more commonly report “air hunger” or a sense of suffocation.

The tempo of onset and the duration of a patient’s dyspnea are likewise helpful in determining the etiology. Acute shortness of breath is usually associated with sudden physiologic changes, such as acute airway narrowing (e.g., laryngeal edema, bronchospasm, or mucus plugging), acute hypoxemia (e.g., pulmonary edema, pneumonia, or pulmonary embolism), or sudden changes in the work of breathing (e.g., pneumothorax). Patients with COPD and idiopathic pulmonary fibrosis (IPF) experience a gradual progression of dyspnea on exertion, punctuated by acute exacerbations of shortness of breath. In contrast, most asthmatics do not have daily symptoms, but experience intermittent episodes of dyspnea, cough, and chest tightness that are usually associated with specific triggers, such as an upper respiratory tract infection or exposure to allergens.

Specific questioning should focus on factors that incite dyspnea as well as on any intervention that helps resolve the patient’s shortness of breath. Asthma is commonly exacerbated by specific triggers, although this can also be true of COPD. Many patients with lung disease report dyspnea on exertion. Determining the degree of activity that results in shortness of breath gives the clinician a gauge of the patient’s degree of disability. Many patients adapt their level of activity to accommodate progressive limitation. For this reason, it is important, particularly in older patients, to delineate the activities in which they engage and how these activities have changed over time. Dyspnea on exertion is often an early symptom of underlying lung or heart disease and warrants a thorough evaluation.

For cough, the clinician should inquire about the duration of the cough, whether or not it is associated with sputum production, and any specific triggers that induce it. Acute cough productive of phlegm is often a symptom of infection of the respiratory system, including processes affecting the upper airway (e.g., sinusitis, tracheitis), the lower airways (e.g., bronchitis, bronchiectasis), and the lung parenchyma (e.g., pneumonia). Both the quantity and quality of the sputum, including whether it is blood-streaked or frankly bloody, should be determined. Hemoptysis warrants urgent evaluation as delineated in **Chap. 39**.

Chronic cough (defined as that persisting for >8 weeks) is commonly associated with obstructive lung diseases, particularly asthma, COPD, and chronic bronchiectasis, as well as “nonrespiratory” diseases, such as gastroesophageal reflux and postnasal drip. Diffuse parenchymal lung diseases, including IPF, frequently present as a persistent, non-productive cough. All causes of cough are not respiratory in origin, and assessment should encompass a broad differential, including cardiac and gastrointestinal diseases as well as psychogenic causes.

Additional Symptoms Patients with respiratory disease may report wheezing, which is suggestive of airways disease, particularly asthma. Hemoptysis can be a symptom of a variety of lung diseases, including infections of the respiratory tract, bronchogenic carcinoma, and pulmonary embolism. In addition, chest pain or discomfort can be respiratory in origin. As the lung parenchyma is not innervated with

pain fibers, pain in the chest from respiratory disorders usually results from either diseases of the parietal pleura (e.g., pneumothorax) or pulmonary vascular diseases (e.g., pulmonary hypertension). As many diseases of the lung can result in strain on the right side of the heart, patients may also present with symptoms of cor pulmonale, including abdominal bloating or distention and pedal edema ([Chap. 257](#)).

Additional History A thorough social history is an essential component of the evaluation of patients with respiratory disease. All patients should be asked about current or previous cigarette smoking, as this exposure is associated with many diseases of the respiratory system, including COPD, bronchogenic lung cancer, and select parenchymal lung diseases (e.g., desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis). For most of these disorders, increased cigarette smoke exposure (i.e., cigarette pack-years) increases the risk of disease. E-cigarette or vaping use can lead to acute or subacute lung injury (i.e., E-cigarette or vaping use-associated lung injury [EVALI]). Secondhand smoke also increases risk for some respiratory disorders, so patients should also be asked about parents, spouses, or housemates who smoke. Possible inhalational exposures at work (e.g., asbestos, silica) or home (e.g., wood smoke, excrement from pet birds) should be explored ([Chap. 289](#)). Travel predisposes to certain infections of the respiratory tract, most notably tuberculosis. Potential exposure to fungi is increased in specific geographic regions or climates (e.g., *Histoplasma capsulatum*), so exposures to these regions should be determined.

Associated symptoms of fever and chills should raise the suspicion of infective etiologies, both pulmonary and systemic. A comprehensive review of systems may suggest rheumatologic or autoimmune disease presenting with respiratory tract manifestations. Questions should focus on joint pain or swelling, rashes, dry eyes, dry mouth, or constitutional symptoms. In addition, carcinomas from a variety of primary sources commonly metastasize to the lung and cause respiratory symptoms. Finally, therapy for other conditions, including both irradiation and medications, can result in diseases of the chest.

Physical Examination The clinician's suspicion of respiratory disease often begins with the patient's vital signs. The respiratory rate is informative, whether elevated (tachypnea) or depressed (hypopnea). In addition, pulse oximetry should be measured, as many patients with respiratory disease have hypoxemia, either at rest or with exertion.

The first step of the physical examination is inspection. Patients with respiratory disease may be in distress and using accessory muscles of respiration to breathe. Severe kyphoscoliosis can result in restrictive pathophysiology. Inability to complete a sentence in conversation is generally a sign of severe impairment and should result in an expedited evaluation of the patient.

Percussion of the chest is used to establish diaphragm excursion and lung size. In the setting of decreased breath sounds, percussion is used to distinguish between pleural effusions (dull to percussion) and pneumothorax (hyper-resonant note).

The role of palpation is limited in the respiratory examination. Palpation can demonstrate subcutaneous air in the setting of barotrauma. It can also be used as an adjunctive assessment to determine whether an area of decreased breath sounds is due to consolidation (increased tactile fremitus) or a pleural effusion (decreased tactile fremitus). To detect unilateral disorders of ventilation, the symmetry and degree of chest wall expansion can be assessed during a deep inspiration by placing one's thumbs together at the midline over the lower posterior chest while grasping the lateral rib cage.

The majority of the manifestations of respiratory disease present as abnormalities of auscultation. Wheezes are a manifestation of airway obstruction. While most commonly a sign of asthma, peribronchial edema in the setting of congestive heart failure can also result in diffuse wheezes, as can any other process that causes narrowing of small airways. Wheezes can be polyphonic, involving multiple different size airways (e.g., asthma), or monophonic, involving one size airway (e.g., bronchogenic carcinoma). For these reasons, clinicians must take care not to attribute all wheezing to asthma.

Rhonchi are a manifestation of obstruction of medium-sized airways, most often with secretions. In the acute setting, this manifestation may be a sign of viral or bacterial bronchitis. Chronic rhonchi suggest bronchiectasis or COPD. In contrast to expiratory wheezes and rhonchi, stridor is a high-pitched, focal inspiratory wheeze, usually heard over the neck as a manifestation of upper airway obstruction.

Crackles, or rales, are commonly a sign of alveolar disease. Processes that fill the alveoli with fluid may result in crackles, including pulmonary edema and pneumonia. Crackles in pulmonary edema are generally more prominent at the bases. Interestingly, diseases that result in fibrosis of the interstitium (e.g., IPF) also result in crackles that sound like Velcro being ripped apart. Although some clinicians make a distinction between "wet" and "dry" crackles, this distinction has not been shown to be a reliable way to differentiate among etiologies of respiratory disease.

One way to help distinguish between crackles associated with alveolar fluid and those associated with interstitial fibrosis is to assess for egophony. *Egophony* is the auscultation of the sound "AH" instead of "EEE" when a patient phonates "EEE." This change in note is due to abnormal sound transmission through consolidated parenchyma and is present in pneumonia but not in IPF. Similarly, areas of alveolar filling have increased whispered pectoriloquy as well as transmission of larger-airway sounds (i.e., bronchial breath sounds in a lung zone where vesicular breath sounds are expected).

The lack or diminution of breath sounds can also help determine the etiology of respiratory disease. Patients with emphysema often have a quiet chest with diffusely decreased breath sounds. A pneumothorax or pleural effusion may present with an area of absent breath sounds.

Other Systems Pedal edema, if symmetric, may suggest cor pulmonale; if asymmetric, it may be due to deep venous thrombosis and associated pulmonary embolism. Jugular venous distention may also be a sign of volume overload associated with right heart failure. *Pulsus paradoxus* is an ominous sign in a patient with obstructive lung disease, as it is associated with significant negative intrathoracic (pleural) pressures required for ventilation and impending respiratory failure.

As stated earlier, rheumatologic disease may manifest primarily as lung disease. Owing to this association, particular attention should be paid to joint and skin examination. Clubbing can be found in many lung diseases, including cystic fibrosis, IPF, and lung cancer. Cyanosis is seen in hypoxic respiratory disorders that result in >5 g of deoxygenated hemoglobin/dL.

DIAGNOSTIC EVALUATION

The sequence of studies is dictated by the clinician's differential diagnosis, as determined by the history and physical examination. Acute respiratory symptoms are often evaluated with multiple tests performed at the same time in order to diagnose any life-threatening diseases rapidly (e.g., pulmonary embolism or multilobar pneumonia). In contrast, chronic dyspnea and cough can be evaluated in a more protracted, stepwise fashion.

Pulmonary Function Testing (See also Chap. 286) The initial pulmonary function test obtained is spirometry. This study is an effort-dependent test used to assess for obstructive pathophysiology as seen in asthma, COPD, and bronchiectasis ([Table 284-1](#)). A diminished-forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) (often defined as <70%) is diagnostic of airflow obstruction. In addition to measuring FEV₁ and FVC, the clinician should examine the flow-volume loop (which is less effort-dependent). A plateau of the inspiratory and expiratory curves suggests large-airway obstruction in extrathoracic and intrathoracic locations, respectively.

Spirometry with symmetric decreases in FEV₁ and FVC warrants further testing, including measurement of lung volumes and the diffusion capacity of the lung for carbon monoxide (DL_{CO}). A total lung capacity <80% of the patient's predicted value defines restrictive pathophysiology. Restriction can result from parenchymal disease, neuromuscular weakness, or chest wall or pleural diseases ([Table 284-1](#)). Restriction with impaired gas exchange, as indicated by a decreased



Edward T. Naureckas, Julian Solway

Dl_{CO} suggests parenchymal lung disease. Additional testing, such as measurements of maximal inspiratory and expiratory pressures, can help diagnose neuromuscular weakness. Normal spirometry, normal lung volumes, and a low Dl_{CO} should prompt further evaluation for pulmonary vascular disease.

Arterial blood gas testing is often helpful in assessing respiratory disease. Hypoxemia, while usually apparent with pulse oximetry, can be further evaluated with the measurement of arterial PO_2 and the calculation of an alveolar gas and arterial blood oxygen tension difference ($[A-a]DO_2$). Patients with diseases that cause ventilation-perfusion mismatch or shunt physiology have an increased $(A-a)DO_2$ at rest. Arterial blood gas testing also allows the measurement of arterial Pco_2 . Hypercarbia can accompany disorders of ventilation, as seen in severe airway obstruction (e.g., COPD) or progressive restrictive physiology.

Chest Imaging (See Chap. A12) Most patients with disease of the respiratory system undergo imaging of the chest as part of the initial evaluation. Clinicians should generally begin with ultrasound of the chest or a plain chest radiograph, preferably posterior-anterior and lateral films. Ultrasound is often readily available and can help rapidly diagnose pneumothorax, pleural effusion, and consolidation of lung parenchyma. Chest radiographs give additional detail and can reveal findings including opacities of the parenchyma, blunting of the costophrenic angles, mass lesions, and volume loss. Of note, many diseases of the respiratory system, particularly those of the airways and pulmonary vasculature, are associated with a normal chest radiograph.

CT scan of the chest can also be useful to delineate parenchymal processes, pleural disease, masses or nodules, and large airways. If the test includes administration of intravenous contrast, the pulmonary vasculature can be assessed with particular utility for determination of pulmonary emboli. Intravenous contrast also allows lymph nodes to be examined in greater detail. When coupled with positron emission tomography (PET), lesions of the chest can be assessed for metabolic activity, helping differentiate between malignancy and scar.

FURTHER STUDIES

Depending on the clinician's suspicion, a variety of other studies may be done. Concern about large-airway lesions may warrant bronchoscopy. This procedure may also be used to sample the alveolar space with bronchoalveolar lavage or to obtain nonsurgical lung biopsies. Blood testing may include assessment for hypercoagulable states in the setting of pulmonary vascular disease, serologic testing for infectious or rheumatologic disease, or assessment of inflammatory markers or leukocyte counts (e.g., eosinophils). Genetic testing is increasingly used for heritable lung diseases such as cystic fibrosis. Sputum evaluation for malignant cells or microorganisms may be appropriate. An echocardiogram to assess right- and left-sided heart function is often obtained. Finally, at times, a surgical lung biopsy is needed to diagnose certain diseases of the respiratory system. All of these studies will be guided by the preceding history, physical examination, pulmonary function testing, and chest imaging.

Acknowledgement

Patricia Kritek contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

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The primary functions of the respiratory system—to oxygenate blood and eliminate carbon dioxide—require virtual contact between blood and fresh air, which facilitates diffusion of respiratory gases between blood and gas. This process occurs in the lung alveoli, where blood flowing through alveolar wall capillaries is separated from alveolar gas by an extremely thin membrane of flattened endothelial and epithelial cells, across which respiratory gases diffuse and equilibrate. Blood flow through the lung is unidirectional via a continuous vascular path along which venous blood absorbs oxygen from and loses CO_2 to inspired gas. The path for airflow, in contrast, reaches a dead end at the alveolar walls; thus, the alveolar space must be ventilated tidally, with inflow of fresh gas and outflow of alveolar gas alternating periodically at the respiratory rate (RR). To provide an enormous alveolar surface area (typically 70 m²) for blood-gas diffusion within the modest volume of a thoracic cavity (typically 7 L), nature has distributed both blood flow and ventilation among millions of tiny alveoli through multigenerational branching of both pulmonary arteries and bronchial airways. Ideally, for the lung to be most efficient in exchanging gas, the fresh gas ventilation of a given alveolus must be matched to its perfusion. However, as a consequence of variations in tube lengths and calibers along these pathways as well as the effects of gravity, tidal pressure fluctuations, and anatomic constraints from the chest wall, the alveoli vary in their relative ventilations and perfusions even in health.

For the respiratory system to succeed in oxygenating blood and eliminating CO_2 , it must be able to ventilate the lung tidally and thus to freshen alveolar gas; it must provide for perfusion of the individual alveolus in a manner proportional to its ventilation; and it must allow adequate diffusion of respiratory gases between alveolar gas and capillary blood. Furthermore, it must accommodate several-fold increases in the demand for oxygen uptake or CO_2 elimination imposed by metabolic needs or acid-base derangement. Given these multiple requirements for normal operation, it is not surprising that many diseases disturb respiratory function. This chapter considers in some detail the physiologic determinants of lung ventilation and perfusion, elucidates how the matching distributions of these processes and rapid gas diffusion allow normal gas exchange, and discusses how common diseases derange these normal functions, thereby impairing gas exchange—or at least increasing the work required by the respiratory muscles or heart to maintain adequate respiratory function.

VENTILATION

It is useful to conceptualize the respiratory system as three independently functioning components: the lung, including its airways; the neuromuscular system; and the chest wall, which includes everything that is not lung or active neuromuscular system. Accordingly, the mass of the respiratory muscles is part of the chest wall, while the force these muscles generate is part of the neuromuscular system; the abdomen (especially an obese abdomen) and the heart (especially an enlarged heart) are, for these purposes, part of the chest wall. Each of these three components has mechanical properties that relate to its enclosed volume (or—in the case of the neuromuscular system—the respiratory system volume at which it is operating) and to the rate of change of its volume (i.e., flow). The work of breathing required of the neuromuscular system is the sum of the work due to volume-related mechanical properties and the work from flow-related mechanical properties required to move air throughout the airways to create this volume change.

Volume-Related Mechanical Properties—Statics **Figure 285-1** shows the volume-related properties of each component of the respiratory system. Because of both surface tension at the air-liquid interface

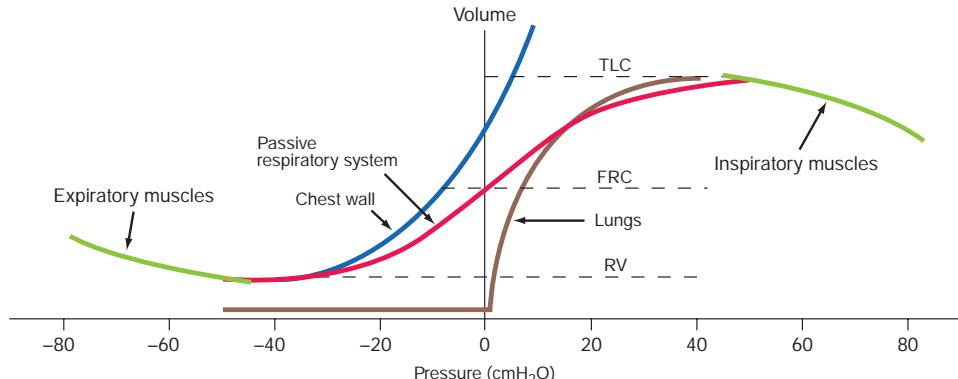


FIGURE 285-1 Pressure-volume curves of the isolated lung, isolated chest wall, combined respiratory system, inspiratory muscles, and expiratory muscles. FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity.

between alveolar wall lining fluid and alveolar gas and elastic recoil of the lung tissue itself, the lung requires a positive transmural pressure difference between alveolar gas and its pleural surface to stay inflated; this difference is called the *elastic recoil pressure* of the lung, and it increases with lung volume. The lung becomes rather stiff at high volumes, so that relatively small volume changes are accompanied by large changes in transpulmonary pressure; in contrast, the lung is compliant at lower volumes, including those at which tidal breathing normally occurs. At zero inflation pressure, even normal lungs retain some air in the alveoli. Because the small peripheral airways are tethered open by outward radial pull from inflated lung parenchyma attached to adventitia, as the lung deflates during exhalation, those small airways are pulled open progressively less, and eventually close, trapping some gas in the alveoli. This effect can be exaggerated with age and especially with obstructive airway diseases, resulting in gas trapping at quite large lung volumes.

The elastic behavior of the passive chest wall (i.e., in the absence of neuromuscular activation) differs markedly from that of the lung. Whereas the lung tends toward full deflation with no distending (transmural) pressure, the chest wall encloses a large volume when pleural pressure equals body surface (atmospheric) pressure. Furthermore, the chest wall is compliant at high enclosed volumes, readily expanding even further in response to increases in transmural pressure. The chest wall also remains compliant at small negative transmural pressures (i.e., when pleural pressure falls slightly below atmospheric pressure), but as the volume enclosed by the chest wall becomes quite small in response to large negative transmural pressures, the passive chest wall becomes stiff due to squeezing together of ribs and intercostal muscles, diaphragm stretch, displacement of abdominal contents, and straining of ligaments and bony articulations. Under normal circumstances, the lung and the passive chest wall enclose essentially the same volume, the only difference being the volumes of the pleural fluid and of the lung parenchyma (normally both quite small in the absence of disease). For this reason and because the lung and chest wall function in mechanical series, the pressure required to displace the passive respiratory system (lungs plus chest wall) at any volume is simply the sum of the elastic recoil pressure of the lungs and the transmural pressure across the chest wall. When plotted against respiratory system volume, this relationship assumes a sigmoid shape, exhibiting stiffness at high lung volumes (imparted by the lung), stiffness at low lung volumes (imparted by the chest wall or sometimes by airway closure), and compliance in the middle range of lung volumes where normal tidal breathing occurs. In addition, a passive resting point of the respiratory system is attained when alveolar gas pressure equals body surface pressure (i.e., when the transrespiratory system pressure is zero). At this volume (called the *functional residual capacity* [FRC]), the outward recoil of the chest wall is balanced exactly by the inward recoil of the lung. As these recoils are transmitted through the pleural fluid, the lung is pulled both outward and inward simultaneously at FRC, and thus, its pressure falls below atmospheric pressure (typically, $-5 \text{ cmH}_2\text{O}$).

The normal passive respiratory system would equilibrate at the FRC and remain there were it not for the actions of the respiratory muscles. The inspiratory muscles act on the chest wall to generate the equivalent of positive pressure across the lungs and passive chest wall, while the expiratory muscles generate the equivalent of negative transrespiratory pressure. The maximal pressures these sets of muscles can generate vary with the lung volume at which they operate. This variation is due to length-tension relationships in striated muscle sarcomeres and to changes in mechanical advantage as the angles of insertion change with lung volume (Fig. 285-1). Nonetheless, under normal conditions, the respiratory muscles are substantially “overpowered” for their roles and generate more than adequate force to drive the respiratory system to its stiffness extremes, as determined by the lung (total lung capacity [TLC]) or by chest wall or airway closure (residual volume [RV]); the airway closure always prevents the adult lung from emptying completely under normal circumstances. The excursion between full and minimal lung inflation is called *vital capacity* (VC; Fig. 285-2) and is readily seen to be the difference between volumes at two unrelated stiffness extremes—one determined by the lung (TLC) and the other by the chest wall or airways (RV). Thus, although VC is easy to measure (see below), it provides little information about the intrinsic properties of the respiratory system. As will become clear, it is much more useful for the clinician to consider TLC and RV individually.

Flow-Related Mechanical Properties—Dynamics The passive chest wall and active neuromuscular system both exhibit mechanical behaviors related to the rate of change of volume, but these behaviors become quantitatively important only at markedly supraphysiologic breathing frequencies (e.g., during high-frequency mechanical ventilation), and thus will not be addressed here. In contrast, the dynamic airflow properties of the lung substantially affect its ability to ventilate and contribute importantly to the work of breathing, and these properties are often deranged by disease. Understanding dynamic airflow properties is, therefore, worthwhile.

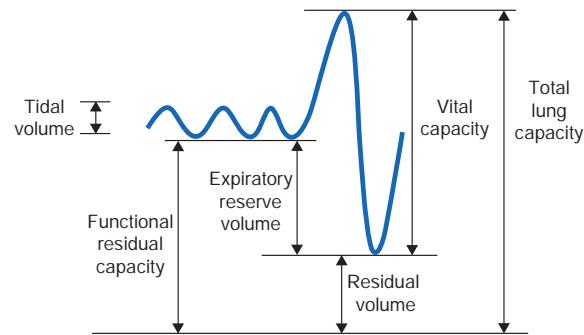


FIGURE 285-2 Spirogram demonstrating a slow vital capacity maneuver and various lung volumes.

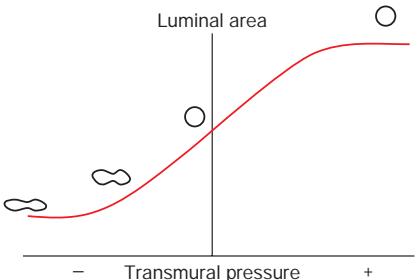


FIGURE 285-3 Luminal area versus transmural pressure relationship. Transmural pressure represents the pressure difference across the airway wall from inside to outside.

As with the flow of any fluid (gas or liquid) in any tube, maintenance of airflow within the pulmonary airways requires a pressure gradient that falls along the direction of flow, the magnitude of which is determined by the flow rate and the frictional resistance to flow. During quiet tidal breathing, the pressure gradients driving inspiratory or expiratory flow are small owing to the very low frictional resistance of normal pulmonary airways (R_{aw} normally $<2 \text{ cmH}_2\text{O/L/s}$). However, during rapid exhalation, another phenomenon reduces flow below that which would have been expected if frictional resistance were the only impediment to flow. This phenomenon is called *dynamic airflow limitation*, and it occurs because the bronchial airways through which air is exhaled are collapsible rather than rigid (Fig. 285-3). An important anatomic feature of the structure of the pulmonary airways is their tree-like branching. While the individual airways in each successive generation, from most proximal (trachea) to most distal (respiratory bronchioles), are smaller than those of the parent generation, their number increases exponentially such that the summed cross-sectional area of the airways becomes very large toward the lung periphery. Because flow (volume/time) is constant along the airway tree, the velocity of airflow (flow/summed cross-sectional area) is much greater in the central airways than in the peripheral airways. During exhalation, gas leaving the alveoli must, therefore, gain velocity as it proceeds toward the mouth. The energy required for this “convective” acceleration is drawn from the component of gas energy manifested as its local pressure, which reduces intraluminal gas pressure, airway transmural

pressure, airway size (Fig. 285-3), and flow. This phenomenon is the Bernoulli effect, the same effect that keeps an airplane airborne, generating a lifting force by decreasing pressure above the curved upper surface of the wing due to acceleration of air flowing over the wing. If an individual attempts to exhale more forcefully, the local velocity increases further and reduces airway size further, resulting in no net increase in flow. Under these circumstances, flow has reached its maximum possible value, or its *flow limit*. Lungs normally exhibit such dynamic airflow limitation. This limitation can be assessed by spirometry, in which an individual inhales fully to TLC and then forcibly exhales to RV. One useful spirometric measure is the volume of air exhaled during the forced expiratory volume in 1 s (FEV₁), as discussed later. Maximal expiratory flow at any lung volume is determined by gas density, airway cross-section and distensibility, elastic recoil pressure of the lung, and frictional pressure loss to the flow-limiting airway site. Under normal conditions, maximal expiratory flow falls with lung volume (Fig. 285-4), primarily because of the dependence of lung recoil pressure on lung volume (Fig. 285-1). In pulmonary fibrosis, lung recoil pressure is increased at any lung volume, and thus the maximal expiratory flow is elevated when considered in relation to lung volume. Conversely, in emphysema, lung recoil pressure is reduced; this reduction is a principal mechanism by which maximal expiratory flows fall. Diseases that narrow the airway lumen at any transmural pressure (e.g., asthma or chronic bronchitis) or that cause excessive airway collapsibility (e.g., tracheomalacia) also reduce maximal expiratory flow.

The Bernoulli effect also applies during inspiration, but the more negative pleural pressures during inspiration lower the pressure outside of the airways, thereby increasing transmural pressure and promoting airway expansion. Thus, inspiratory airflow limitation seldom occurs due to diffuse pulmonary airway disease. Conversely, extrathoracic airway narrowing (e.g., due to a tracheal adenoma or post-tracheostomy stricture) can lead to inspiratory airflow limitation (Fig. 285-4).

The Work of Breathing In health, the elastic (volume change-related) and dynamic (flow-related) loads that must be overcome to ventilate the lungs at rest are small, and the work required of the respiratory muscles is minimal. However, the work of breathing can increase considerably due to a metabolic requirement for substantially increased ventilation, an abnormally increased mechanical load, or both. As discussed below, the rate of ventilation is primarily set by the need to eliminate

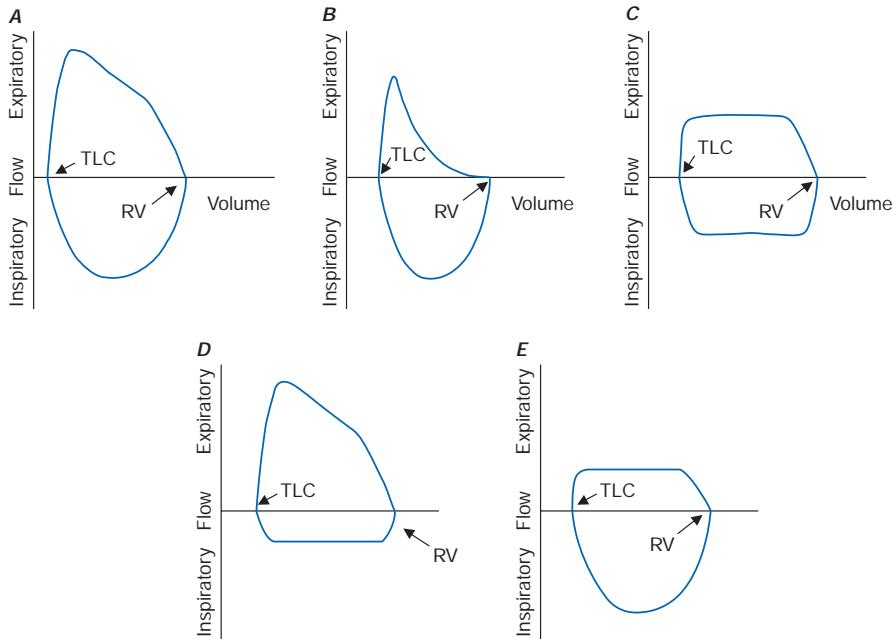


FIGURE 285-4 Flow-volume loops. **A.** Normal. **B.** Airflow obstruction. **C.** Fixed central airway obstruction (either above or below the thoracic inlet). **D.** Variable upper airway obstruction (above the thoracic inlet). **E.** Variable lower airway obstruction (below the thoracic inlet). RV, residual volume; TLC, total lung capacity.

carbon dioxide, and thus, ventilation increases during exercise (sometimes by >20-fold) and during metabolic acidosis as a compensatory response. Naturally, the work rate required to overcome the elasticity of the respiratory system increases with both the depth and the frequency of tidal breaths, while the work required to overcome the dynamic load increases with total ventilation. A modest increase of ventilation is most efficiently achieved by increasing tidal volume but not RR, which is the normal ventilatory response to lower-level exercise. At higher levels of exercise, deep breathing persists, but RR also increases.

The work of breathing also increases when disease reduces the compliance of the respiratory system or increases the resistance to airflow. The former occurs commonly in diseases of the lung parenchyma (interstitial processes or fibrosis, alveolar filling diseases such as pulmonary edema or pneumonia, or substantial lung resection), and the latter occurs in obstructive airway diseases such as asthma, chronic bronchitis, emphysema, and cystic fibrosis. Furthermore, severe airflow obstruction can functionally reduce the compliance of the respiratory system by leading to dynamic hyperinflation. In this scenario, expiratory flows slowed by the obstructive airways disease may be insufficient to allow complete exhalation during the expiratory phase of tidal breathing; as a result, the “functional residual capacity (FRC)” from which the next breath is inhaled is greater than the static FRC. With repetition of incomplete exhalations of each tidal breath, the operating FRC becomes dynamically elevated, sometimes to a level that approaches TLC. At these high lung volumes, the respiratory system is much less compliant than at normal breathing volumes, and thus, the elastic work of each tidal breath is also increased. The dynamic pulmonary hyperinflation that accompanies severe airflow obstruction causes patients to sense difficulty in inhaling—even though the root cause of this pathophysiologic abnormality is expiratory airflow obstruction.

Adequacy of Ventilation As noted above, the respiratory control system that sets the rate of ventilation responds to chemical signals, including arterial CO₂ and oxygen tensions and blood pH, and to volitional needs, such as the need to inhale deeply before playing a long phrase on the trumpet. Disturbances in ventilation are discussed in Chap. 296. The focus of this chapter is on the relationship between ventilation of the lung and CO₂ elimination.

At the end of each tidal exhalation, the conducting airways are filled with alveolar gas that did not reach the mouth when expiratory flow stopped. During the ensuing inhalation, fresh gas immediately enters the airway tree at the mouth, but the gas first entering the alveoli at the start of inhalation is that same alveolar gas in the conducting airways that had just left the alveoli. Accordingly, fresh gas does not enter the alveoli until the volume of the conducting airways has been inspired. This volume is called the *anatomic dead space* (V_D). Quiet breathing with tidal volumes smaller than the anatomic dead space introduces no fresh gas into the alveoli at all; only that part of the inspired tidal volume (V_I) that is greater than the V_D introduces fresh gas into the alveoli. The dead space can be further increased functionally if some of the inspired tidal volume is delivered to a part of the lung that receives no pulmonary blood flow and thus cannot contribute to gas exchange (e.g., the portion of the lung distal to a large pulmonary embolus). In this situation, exhaled minute ventilation (V_E = V_T × RR) includes a component of dead space ventilation (V_D = V_T × RR) and a component of fresh gas alveolar ventilation (V_A = [V_T - V_D] × RR). CO₂ elimination from the alveoli is equal to V_A times the difference in CO₂ fraction between inspired air (essentially zero) and alveolar gas (typically ~5.6% after correction for humidification of inspired air, corresponding to 40 mmHg). In the steady state, the alveolar fraction of CO₂ is equal to metabolic CO₂ production divided by alveolar ventilation. Because, as discussed below, alveolar and arterial CO₂ tensions are equal, and because the respiratory controller normally strives to maintain arterial Pco₂ (Paco₂) at ~40 mmHg, the adequacy of alveolar ventilation is reflected in Paco₂. If the Paco₂ falls much below 40 mmHg, alveolar hyperventilation is present; if the Paco₂ exceeds 40 mmHg, alveolar hypoventilation is present. Ventilatory failure is characterized by extreme alveolar hypoventilation.

As a consequence of oxygen uptake of alveolar gas into capillary blood, alveolar oxygen tension falls below that of inspired gas. The rate

of oxygen uptake (determined by the body's metabolic oxygen consumption) is related to the average rate of metabolic CO₂ production, and their ratio—the “respiratory quotient” (R = VCO₂/VO₂)—depends largely on the fuel being metabolized. For a typical American diet, R is usually around 0.85. Together, these phenomena allow the estimation of alveolar oxygen tension, according to the following relationship, known as the *alveolar gas equation*:

$$Pao_2 = Fio_2 \times (P_{bar} - Ph_2O) - Paco_2/R$$

The alveolar gas equation also highlights the influences of inspired oxygen fraction Fio₂, barometric pressure (P_{bar}), and vapor pressure of water (Ph₂O = 47 mmHg at 37°C) in addition to alveolar ventilation (which sets Paco₂) in determining Pao₂. An implication of the alveolar gas equation is that severe arterial hypoxemia rarely occurs as a pure consequence of alveolar hypoventilation at sea level while an individual is breathing air. The potential for alveolar hypoventilation to induce severe hypoxemia with otherwise normal lungs increases as P_{bar} falls with increasing altitude.

GAS EXCHANGE

Diffusion For oxygen to be delivered to the peripheral tissues, it must pass from alveolar gas into alveolar capillary blood by diffusing through alveolar membrane. The aggregate alveolar membrane is highly optimized for this process, with a very large surface area and minimal thickness. Diffusion through the alveolar membrane is so efficient in the human lung that in most circumstances hemoglobin of a red blood cell becomes fully oxygen saturated by the time the cell has traveled just one-third the length of the alveolar capillary. Thus, the uptake of alveolar oxygen is ordinarily limited by the amount of blood transiting the alveolar capillaries rather than by the rapidity with which oxygen can diffuse across the membrane; consequently, oxygen uptake from the lung is said to be “perfusion limited” rather than diffusion limited. CO₂ also equilibrates rapidly across the alveolar membrane. Therefore, the oxygen and CO₂ tensions in capillary blood leaving a normal alveolus are essentially equal to those in alveolar gas. Only in rare circumstances (e.g., at high altitude or in high-performance athletes exerting maximal effort) is oxygen uptake from normal lungs diffusion limited. Diffusion limitation can also occur in interstitial lung disease if substantially thickened alveolar walls remain perfused.

Ventilation/Perfusion Heterogeneity As noted above, for gas exchange to be most efficient, ventilation to each individual alveolus (among the millions of alveoli) should match perfusion to its accompanying capillaries. Because of the differential effects of gravity on lung mechanics and blood flow throughout the lung and because of differences in airway and vascular architecture among various respiratory paths, there is minor ventilation/perfusion heterogeneity even in the normal lung; however, V/Q heterogeneity can be particularly marked in disease. Two extreme examples are (1) ventilation of unperfused lung distal to a pulmonary embolus, in which ventilation of the physiologic dead space is “wasted” in the sense that it does not contribute to gas exchange; and (2) perfusion of nonventilated lung (a “shunt”), which allows venous blood to pass through the lung unaltered. When mixed with fully oxygenated blood leaving other well-ventilated lung units, shunted venous blood disproportionately lowers the mixed arterial Pao₂ as a result of the nonlinear oxygen content versus PO₂ relationship of hemoglobin (Fig. 285-5). Furthermore, the resulting arterial hypoxemia is refractory to supplemental inspired oxygen. The reason is that (1) raising the inspired Fio₂ has no effect on alveolar gas tensions in nonventilated alveoli and (2) while raising inspired Fio₂ increases Paco₂ in ventilated alveoli, the oxygen content of blood exiting ventilated units increases only slightly, as hemoglobin will already have been nearly fully saturated and the solubility of oxygen in plasma is quite small.

A more common occurrence than the two extreme examples given above is a widening of the distribution of ventilation/perfusion ratios; such V/Q heterogeneity is a common consequence of lung disease. In this circumstance, perfusion of relatively underventilated alveoli

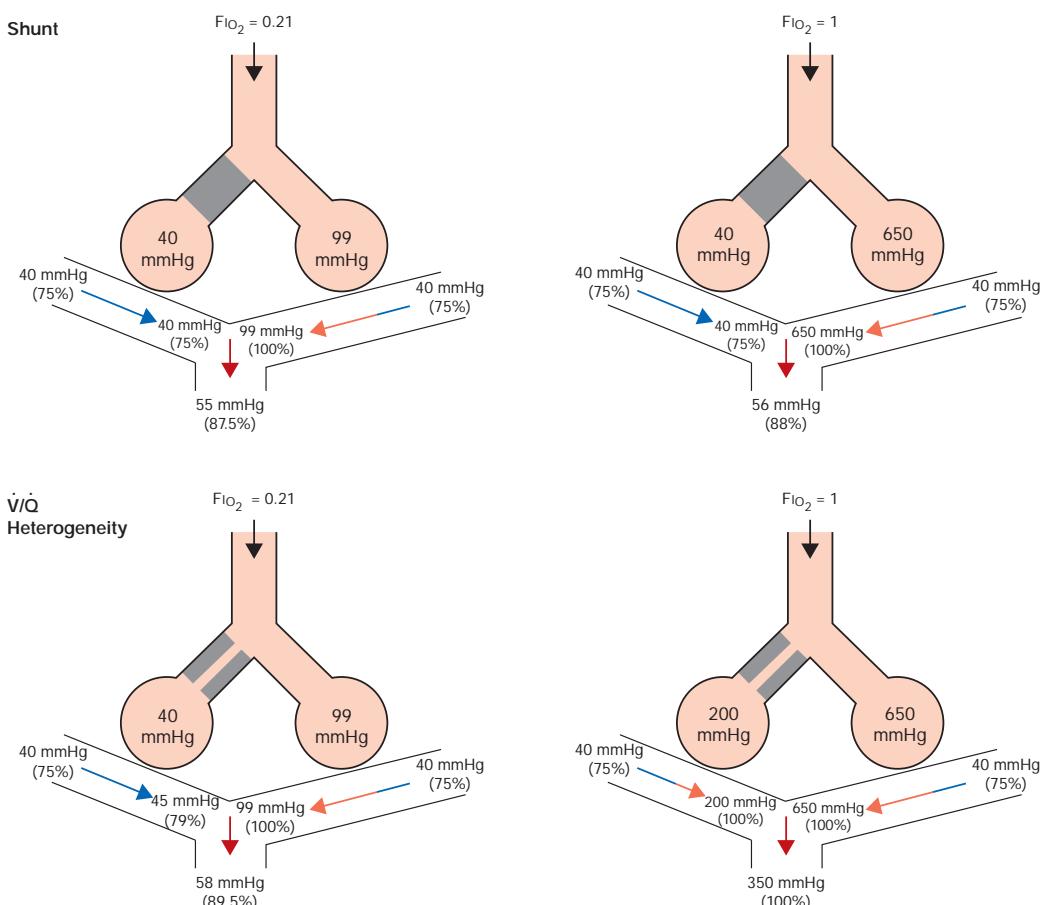


FIGURE 285-5 Influence of air versus oxygen breathing on mixed arterial oxygenation in shunt and ventilation/perfusion heterogeneity. Partial pressure of oxygen (mmHg) and oxygen saturations are shown for mixed venous blood, for end capillary blood (normal vs. affected alveoli), and for mixed arterial blood. FIO_2 , fraction of inspired oxygen; \dot{V}/\dot{Q} , ventilation/perfusion.

results in the incomplete oxygenation of exiting blood. When mixed with well-oxygenated blood leaving higher \dot{V}/\dot{Q} regions, this partially reoxygenated blood disproportionately lowers arterial PaO_2 , although to a lesser extent than does a similar perfusion fraction of blood leaving regions of pure shunt. In addition, in contrast to shunt regions, inhalation of supplemental oxygen raises the PaO_2 even in relatively underventilated low \dot{V}/\dot{Q} regions, and so the arterial hypoxemia induced by \dot{V}/\dot{Q} heterogeneity is typically responsive to oxygen therapy (Fig. 285-5).

In sum, arterial hypoxemia can be caused by substantial reduction of inspired oxygen tension, severe alveolar hypoventilation, perfusion of relatively underventilated (low \dot{V}/\dot{Q}) or completely unventilated (shunt) lung regions, and, in very unusual circumstances, limitation of gas diffusion.

PATOPHYSIOLOGY

Although many diseases injure the respiratory system, this system responds to injury in relatively few ways. For this reason, the pattern of physiologic abnormalities may or may not provide sufficient information by which to discriminate among conditions.

Figure 285-6 lists abnormalities in pulmonary function testing that are typically found in a number of common respiratory disorders and highlights the simultaneous occurrence of multiple physiologic abnormalities. The coexistence of some of these respiratory disorders results in more complex superposition of these abnormalities. Methods to measure respiratory system function clinically are described later in this chapter.

Ventilatory Restriction due to Increased Elastic Recoil—

Example: Idiopathic Pulmonary Fibrosis Idiopathic pulmonary fibrosis raises lung recoil at all lung volumes, thereby lowering TLC, FRC, and RV as well as forced vital capacity (FVC). Maximal expiratory

flows are also reduced from normal values but are elevated when considered in relation to lung volumes. Increased flow occurs both because the increased lung recoil drives greater maximal flow at any lung volume and because airway diameters are relatively increased due to greater radially outward traction exerted on bronchi by the stiff lung parenchyma. For the same reason, airway resistance is also normal. Destruction of the pulmonary capillaries by the fibrotic process results in a marked reduction in diffusing capacity (see below). Oxygenation is often severely reduced by persistent perfusion of alveolar units that are relatively underventilated due to fibrosis of nearby (and mechanically linked) lung due to those alveolar units already being stretched to their maximum volume with little further increase in volume with inspiration. The flow-volume loop (see below) looks like a miniature version of a normal loop but is shifted toward lower absolute lung volumes and displays maximal expiratory flows that are increased for any given volume over the normal tracing.

Ventilatory Restriction due to Chest Wall Abnormality—

Example: Moderate Obesity As the size of the average American continues to increase, this pattern may become the most common of pulmonary function abnormalities. In moderate obesity, the outward recoil of the chest wall is blunted by the weight of chest wall fat and the space occupied by intraabdominal fat. In this situation, preserved inward recoil of the lung overbalances the reduced outward recoil of the chest wall, and FRC falls. Because respiratory muscle strength and lung recoil remain normal, TLC is typically unchanged (although it may fall in massive obesity) and RV is normal (but may be reduced in massive obesity). Mild hypoxemia may be present due to perfusion of alveolar units that are poorly ventilated because of airway closure in dependent portions of

	Restriction due to increased lung elastic recoil (pulmonary fibrosis)	Restriction due to chest wall abnormality (moderate obesity)	Restriction due to respiratory muscle weakness (myasthenia gravis)	Obstruction due to airway narrowing (acute asthma)	Obstruction due to decreased elastic recoil (severe emphysema)
TLC	60%	95%	75%	100%	130%
FRC	60%	65%	100%	104%	220%
RV	60%	100%	120%	120%	310%
FVC	60%	92%	60%	90%	60%
FEV ₁	75%	92%	60%	35% pre-b.d. 75% post-b.d.	35% pre-b.d. 38% post-b.d.
R _{aw}	1.0	1.0	1.0	2.5	1.5
D _{LCO}	60%	95%	80%	120%	40%

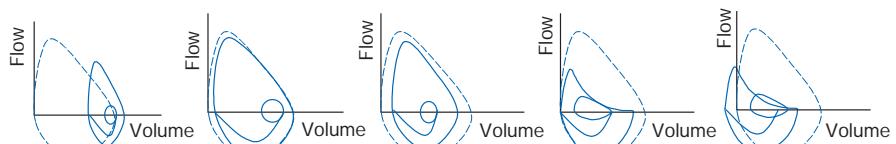


FIGURE 285-6 Common abnormalities of pulmonary function (see text). Pulmonary function values are expressed as a percentage of normal predicted values, except for R_{aw} , which is expressed as $\text{cmH}_2\text{O/L/s}$ (normal, $<2 \text{ cmH}_2\text{O/L/s}$). The figures at the bottom of each column show the typical configuration of flow-volume loops in each condition, including the flow-volume relationship during tidal breathing. b.d., bronchodilator; D_{LCO}, diffusion capacity of lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; R_{aw}, airways resistance; RV, residual volume; TLC, total lung capacity.

the lung during breathing near the reduced FRC. Flows remain normal, as does the diffusion capacity of the lung for carbon monoxide D_{LCO} unless obstructive sleep apnea (which often accompanies obesity) and associated chronic intermittent hypoxemia have induced pulmonary arterial hypertension, in which case D_{LCO} may be low.

Ventilatory Restriction due to Reduced Muscle Strength—Example: Myasthenia Gravis In this circumstance, FRC remains normal, as both lung recoil and passive chest wall recoil are normal. However, TLC is low and RV is elevated because respiratory muscle strength is insufficient to push the passive respiratory system fully toward either volume extreme. Caught between the low TLC and the elevated RV, FVC and FEV₁ are reduced as “innocent bystanders.” As airway size and lung vasculature are unaffected, both R_{aw} and D_{LCO} are normal. Oxygenation is normal unless weakness becomes so severe that the patient has insufficient strength to reopen collapsed alveoli during sighs, with resulting atelectasis.

Airflow Obstruction due to Decreased Airway Diameter—Example: Acute Asthma During an episode of acute asthma, luminal narrowing due to smooth muscle constriction as well as inflammation and thickening within the small- and medium-sized bronchi raise frictional resistance and reduce airflow. “Scooping” of the flow-volume loop is caused by reduction of airflow, especially at lower lung volumes. Often, airflow obstruction can be reversed by inhalation of β_2 -adrenergic agonists acutely or by treatment with inhaled steroids chronically. TLC usually remains normal (although elevated TLC is sometimes seen in long-standing asthma), but FRC may be dynamically elevated. RV is often increased due to exaggerated airway closure at low lung volumes, and this elevation of RV reduces FVC. Because central airways are narrowed, R_{aw} is usually elevated. Mild arterial hypoxemia is often present due to perfusion of relatively underventilated alveoli distal to obstructed airways (and is responsive to oxygen supplementation), but D_{LCO} is normal or mildly elevated.

Airflow Obstruction due to Decreased Elastic Recoil—Example: Severe Emphysema Loss of lung elastic recoil in severe emphysema results in pulmonary hyperinflation, of which elevated TLC is the hallmark. FRC is more severely elevated due to both loss of lung elastic recoil and dynamic hyperinflation—the same

phenomenon as auto-PEEP (auto-positive end-expiratory pressure), which is the positive end-expiratory alveolar pressure that occurs when a new breath is initiated before the lung volume is allowed to return to FRC. RV is very severely elevated because of airway closure and because exhalation toward RV may take so long that RV cannot be reached before the patient must inhale again. Both FVC and FEV₁ are markedly decreased, the former because of the severe elevation of RV and the latter because loss of lung elastic recoil reduces the pressure driving maximal expiratory flow and also reduces tethering open of small intrapulmonary airways. The flow-volume loop demonstrates marked scooping, with an initial transient spike of flow attributable largely to expulsion of air from collapsing central airways at the onset of forced exhalation. Otherwise, the central airways remain relatively unaffected, so R_{aw} is normal in “pure” emphysema. Loss of alveolar surface and capillaries in the alveolar walls reduces D_{LCO}; however, because poorly ventilated emphysematous acini are also poorly perfused (due to loss of their capillaries), arterial hypoxemia usually is not seen at rest until emphysema becomes very severe. However, during exercise, Pao₂ may fall precipitously if extensive destruction of the pulmonary vasculature prevents a sufficient increase in cardiac output and mixed venous oxygen content falls substantially. Under these circumstances, any venous admixture through low V/Q units has a particularly marked effect in lowering mixed arterial oxygen tension.

FUNCTIONAL MEASUREMENTS

Measurement of Ventilatory Function • LUNG VOLUMES Figure 285-2 demonstrates spiroometry tracing in which the volume of air entering or exiting the lung is plotted over time. In a slow vital capacity maneuver, the patient inhales from FRC, fully inflating the lungs to TLC, and then exhales slowly to RV; VC, the difference between TLC and RV, represents the maximal excursion of the respiratory system. Spirometry discloses relative volume changes during these maneuvers but cannot reveal the absolute volumes at which they occur. To determine absolute lung volumes, two approaches are commonly used: inert gas dilution and body plethysmography. In the former, a known amount of a nonabsorbable inert gas (usually helium or neon) is inhaled in a single large breath or is rebreathed from a closed circuit; the inert gas is diluted by the gas resident in the lung at the time of inhalation, and its final concentration reveals the volume

of resident gas contributing to the dilution. A drawback of this method is that regions of the lung that ventilate poorly (e.g., due to airflow obstruction) may not receive much inspired inert gas and so do not contribute to its dilution. Therefore, inert gas dilution (especially in the single-breath method) often underestimates true lung volumes.

In the second approach, FRC is determined by measuring the compressibility of gas within the chest, which is proportional to the volume of gas being compressed. The patient sits in a body plethysmograph (a chamber usually made of transparent plastic to minimize claustrophobia) and, at the end of a normal tidal breath (i.e., when lung volume is at FRC), is instructed to pant against a closed shutter, thus periodically compressing air within the lung slightly. Pressure fluctuations at the mouth and volume fluctuations within the body box (equal but opposite to those in the chest) are determined, and from these measurements, the thoracic gas volume is calculated by means of Boyle's law. Once FRC is obtained, TLC and RV are calculated by adding the value for inspiratory capacity and subtracting the value for expiratory reserve volume, respectively (both values having been obtained during spirometry) (Fig. 285-2). The most important determinants of healthy individuals' lung volumes are height, age, and sex, but there is considerable additional normal variation beyond that accounted for by these parameters. In addition, race influences lung volumes; on average, TLC values are ~12% lower in African Americans and 6% lower in Asian Americans than in Caucasian Americans. In practice, a mean "normal" value is predicted by multivariate regression equations using height, age, and sex, and the patient's value is divided by the predicted value (often with "race correction" applied) to determine "percent predicted." For most measures of lung function, 85–115% of the predicted value can be normal; however, in health, the various lung volumes tend to scale together. For example, if one is "normal big" with a TLC 110% of the predicted value, all other lung volumes and spirometry values will also approximate 110% of their respective predicted values. This pattern is particularly helpful in evaluating airflow, as discussed below.

AIR FLOW As noted above, spirometry plays a key role in lung volume determination. Even more often, spirometry is used to measure airflow, which reflects the dynamic properties of the lung. During an FVC maneuver, the patient inhales to TLC and then exhales rapidly and forcefully to RV; this method ensures that flow limitation has been achieved, so that the precise effort made has little influence on actual flow. The total amount of air exhaled is the FVC, and the amount of air exhaled in the first second is the FEV₁; the FEV₁ is a flow rate, revealing volume change per time. Like lung volumes, an individual's maximal expiratory flows should be compared with predicted values based on height, age, and sex. While the FEV₁/FVC ratio is typically reduced in airflow obstruction, this condition can also reduce FVC by raising RV, sometimes rendering the FEV₁/FVC ratio "artifactually normal" with the erroneous implication that airflow obstruction is absent. To circumvent this problem, it is useful to compare FEV₁ as a fraction of its predicted value with TLC as a fraction of its predicted value. In health, the results are usually similar. In contrast, even an FEV₁ value that is 95% of its predicted value may actually be relatively low if TLC is 110% of its respective predicted value. In this case, airflow obstruction may be present, despite the "normal" value for FEV₁.

The relationships among volume, flow, and time during spirometry are best displayed in two plots—the spirogram (volume vs time) and the flow-volume loop (flow vs volume) (Fig. 285-4). In conditions that cause airflow obstruction, the site of obstruction is sometimes correlated with the shape of the flow-volume loop. In diseases that cause lower airway obstruction, such as asthma and emphysema, flows decrease more rapidly with declining lung volumes, leading to a characteristic scooping of the flow-volume loop. In contrast, fixed upper-airway obstruction typically leads to inspiratory and/or expiratory flow plateaus (Fig. 285-4).

AIRWAYS RESISTANCE The total resistance of the pulmonary and upper airways is measured in the same body plethysmograph used to measure FRC. The patient is asked once again to pant, but this time against a closed and then opened shutter. Panting against the closed shutter reveals the thoracic gas volume as described above. When

the shutter is opened, flow is directed to and from the body box, so that volume fluctuations in the box reveal the extent of thoracic gas compression, which in turn reveals the pressure fluctuations driving flow. Simultaneous measurement of flow allows the calculation of lung resistance (as flow divided by pressure). In health, R_{aw} is very low (<2 cmH₂O/L/s), and half of the detected resistance resides within the upper airway. In the lung, most resistance originates in the central airways. For this reason, airways resistance measurement tends to be insensitive to peripheral airflow obstruction.

RESPIRATORY MUSCLE STRENGTH To measure respiratory muscle strength, the patient is instructed to exhale or inhale with maximal effort against a closed shutter while pressure is monitored at the mouth. Pressures >±60 cmH₂O at FRC are considered adequate and make it unlikely that respiratory muscle weakness accounts for any other resting ventilatory dysfunction that is identified.

Measurement of Gas Exchange • DIFFUSING CAPACITY (DLco) This test uses a small (and safe) amount of carbon monoxide (CO) to measure gas exchange across the alveolar membrane during a 10-s breath hold. CO in exhaled breath is analyzed to determine the quantity of CO crossing the alveolar membrane and combining with hemoglobin in red blood cells. This "single-breath diffusing capacity" (DLco) value increases with the surface area available for diffusion and the amount of hemoglobin within the capillaries, and it varies inversely with alveolar membrane thickness. Thus, DLco decreases in diseases that thicken or destroy alveolar membranes (e.g., pulmonary fibrosis, emphysema), curtail the pulmonary vasculature (e.g., pulmonary hypertension), or reduce alveolar capillary hemoglobin (e.g., anemia). Single-breath diffusing capacity may be elevated in acute congestive heart failure, asthma, polycythemia, and pulmonary hemorrhage.

Arterial Blood Gases The effectiveness of gas exchange can be assessed by measuring the partial pressures of oxygen and CO₂ in a sample of blood obtained by arterial puncture. The oxygen content of blood (CaO₂) depends on arterial saturation (%O₂ Sat), which is set by Pao₂, pH, and Paco₂ according to the oxyhemoglobin dissociation curve. CaO₂ can also be measured by oximetry (see below):

$$\text{CaO}_2 \text{ (mL/dL)} = 1.39 \text{ (mL/dL)} \times [\text{hemoglobin}] \text{ (g)} \times \% \text{ O}_2 \text{ Sat} \\ + 0.003 \text{ (mL/dL/mmHg)} \times \text{Pao}_2 \text{ (mmHg)}$$

If hemoglobin saturation alone needs to be determined, this task can be accomplished noninvasively with pulse oximetry.

Acknowledgment

The authors wish to acknowledge the contributions of Drs. Steven E. Weinberger and Irene M. Rosen to this chapter in previous editions.

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FIGURE 286-1 Thoracoscopy demonstrating numerous parietal pleural nodules in a patient with sarcoidosis-related pleural disease. Pleural biopsy revealed nonnecrotizing granulomas. (Source: Majid Shafiq, MD, MPH)

Diagnostic procedures in respiratory disease encompass a wide array of invasive and noninvasive modalities. Methods for acquiring diagnostic specimens are described in this chapter, as are the various imaging modalities at hand. **Pulmonary function tests and measurements of gas exchange are described in Chap. 284.**

BEDSIDE PLEURAL PROCEDURES

THORACENTESIS

Thoracentesis, also known as pleurocentesis, refers to percutaneous aspiration of fluid from the pleural space. The right and left pleural spaces do not normally communicate with each other, and either can be directly accessed between the thoracic ribs. The current standard of care entails using point-of-care ultrasonography to mark the site of needle puncture; this reduces the risks of “dry tap” as well as complications such as pneumothorax. Beside palliation of symptoms associated with pleural effusion (most commonly dyspnea), thoracentesis may be performed for diagnostic purposes. The range of hematologic, biochemical, microbiologic, and cytologic pleural fluid studies has largely remained unchanged over the past few decades, as has the widespread adoption of Light’s criteria for distinguishing exudates from transudates that were described in 1972. However, newer assays such as mesothelin-1 testing for neoplastic diseases (chiefly mesothelioma) have also become available more recently. **More details on pleural fluid testing are described in Chap. 294.**

CLOSED PLEURAL BIOPSY

Closed pleural biopsy involves percutaneous sampling of the parietal pleural lining. This procedure can be performed either “blindly” (typically with an Abrams needle) or by using imaging guidance such as CT or ultrasound. Closed pleural biopsy without ultrasound guidance is highly sensitive for pleural tuberculosis, owing to the diffuse pleural involvement that is typically seen in those cases.

Image-guided closed pleural biopsy is most helpful in case of focal pleural abnormalities such as pleural nodules, which are virtually pathognomonic of malignant involvement. Limited studies have shown high diagnostic yields of around 80–90% with this modality, but patient selection is key as the diagnostic performance may be considerably lower in the absence of a specific pleural abnormality that could be visualized. Between CT and ultrasound imaging, only ultrasound is typically performed in real-time during the act of obtaining the biopsy.

THORACIC SURGICAL PROCEDURES

THORACOSCOPY AND THORACOTOMY

Thoracoscopy and thoracotomy encompass a spectrum of surgical procedures that involve accessing and operating within the pleural space, either via one or more small entry ports using thoracoscopic tools or via larger incisions as in thoracotomy (Fig. 286-1). Thoracoscopy varies in its scope considerably. An interventional pulmonologist typically performs a pleuroscopy (also known as *medical thoracoscopy*) and accesses the pleural space through a single port for parietal pleural biopsy or for limited therapeutic purposes such as minor lysis of adhesions, thoracoscopic pleurodesis, or indwelling pleural catheter placement. This procedure can usually be performed safely under conscious sedation. On the other hand, video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) represent more invasive procedures but with more controlled environments entailing general anesthesia with single-lung ventilation, creation of multiple entry ports, and several additional diagnostic and therapeutic

possibilities including, but not limited to, lung biopsy, lymph node sampling, lobectomy, decortication, and creation of a pericardial window. Open thoracotomy uses wider incisions and more conventional surgical techniques for performing all of the above as well as additional tasks such as creation of a Clagett window for chronic bronchopleural fistula with empyema.

MEDIASTINOSCOPY AND MEDIASTINOTOMY

Surgical access to the mediastinum, either through a small port (mediastinoscopy) or a wider incision (mediastinotomy), enables diagnostic sampling of mediastinal structures such as mediastinal lymph nodes as part of lung cancer staging. With the advent of endoscopic needle-based techniques (see below), surgery is no longer considered the first-line option for diagnostic lymph node sampling but is recommended in cases of negative needle-based sampling where suspicion for malignant nodal involvement remains sufficiently high.

BRONCHOSCOPY

Bronchoscopy, which entails passing a tube with a lighted camera inside the lower respiratory tract, includes flexible and rigid bronchoscopy (termed after the physical properties of each bronchoscope). Flexible bronchoscopy is by far the more commonly used form and enables access to more distal parts of the respiratory tract. The rigid bronchoscope, although limited to the central airways, has the added advantage of providing a secure airway for ventilation; artificial breaths can then be administered through the scope itself as part of a closed circuit or through open jet ventilation. The rigid bronchoscope also provides a conduit for diagnostic or therapeutic instruments to be passed freely, rather than through the relatively constrained working channel of a flexible bronchoscope. When bronchoscopy is limited to diagnostic indications, the rigid bronchoscope is seldom used except on occasion as a precautionary measure for anticipated severe bleeding where having a more secure airway might be particularly advantageous (e.g., in transbronchial cryobiopsy). Different types of diagnostic bronchoscopic procedures are described below.

Bronchoalveolar Lavage Bronchoalveolar lavage (BAL) is the gold standard method for obtaining respiratory secretions for hematologic, biochemical, microbiological, and/or cytologic analyses. It avoids the risk of salivary contamination, which may be seen in a sputum specimen, and is particularly useful when sputum cannot be obtained or when sampling of a specific pulmonary lobe or segment is desired. After wedging the bronchoscope in a distal airway in order to prevent fluid escape around the scope, sterile saline or distilled water is instilled through the scope’s working channel (typically in one to three aliquots of approximately 50 mL each). Immediately thereafter, suction is applied to aspirate as much of the fluid as possible. This allows sampling of distal airways and lung parenchyma—areas not directly viewable or accessible. If there is concern for alveolar hemorrhage, serial BALs from the same site may show rising red blood cell counts and even visibly bloodier returns with subsequent lavages.

Brushing and Endobronchial Biopsy Bronchoscopy brushing is a minimally invasive sampling technique that can be used to sample the mucosal biofilm for microbiologic analyses as well as the bronchial epithelial layer for cytologic analyses. Endobronchial biopsy allows sampling of abnormal bronchial mucosa and submucosa for histopathologic analysis (as may be indicated in cases of endobronchial amyloidosis or sarcoidosis, for example). Among cigarette smokers with one or more lung nodules and a nondiagnostic bronchoscopy, bronchial brushings can be used with a commercially available classifier that estimates lung cancer probability based on a gene expression signature. Patients with intermediate pretest probability who end up with low posttest probability can more confidently opt for imaging surveillance, thus avoiding further invasive testing and related complications.

Transbronchial Biopsy Including Cryobiopsy Transbronchial biopsy involves removing a piece of alveolated lung tissue by passing a sampling tool into the alveolar space. The most commonly employed biopsy tool is flexible forceps, typically 2.0 mm or 2.8 mm in caliber. When a specific pulmonary lesion such as a lung nodule is being biopsied, various imaging and navigation tools (described below) may be used to help guide the site of forceps biopsy. When random sampling of the lung parenchyma is desired, e.g., to assess for posttransplant lung rejection, either fluoroscopic guidance or tactile feedback is commonly used to position the forceps in the subpleural lung parenchyma. Limited data point to three biopsy samples being adequate for optimizing sensitivity in case of malignant lung nodules. On the other hand, at least five distinct pieces of alveolated lung tissue are needed for formal diagnosis of acute cellular rejection among lung transplant recipients per current recommendations. An increasingly popular biopsy tool is the cryoprobe, a flexible catheter with a blunt tip that delivers liquid nitrogen or carbon dioxide over a few seconds to freeze a portion of lung parenchyma and make it adhere to the probe itself. Before the tissue can thaw and detach, the probe is pulled back (typically along with

the bronchoscope itself), and a frozen piece of lung tissue is removed alongside. Cryobiopsy has a higher diagnostic yield than forceps biopsy for diffuse parenchymal illnesses such as idiopathic pulmonary fibrosis but comes with a higher risk of major bleeding and pneumothorax.

Transbronchial Needle Aspiration Transbronchial needle aspiration (TBNA) involves using a hollow-bore needle for obtaining aspirated specimens. This may be accompanied by suction or simply rely on capillary action, with data not pointing to suction impacting diagnostic sensitivity. TBNA has diagnostic sensitivity superior to that of transbronchial biopsy for malignant peripheral nodules. This makes intuitive sense given that the lesion may lie extraluminally and require traversing the airway wall, which only the needle may be able to accomplish. Furthermore, combining TBNA with conventional transbronchial biopsy appears to increase pooled diagnostic sensitivity.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Endobronchial ultrasound (EBUS) and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) represent a major advance in diagnostic bronchoscopy over the turn of the twentieth century, largely replacing surgical methods for lymph node sampling. EBUS-TBNA involves using a specialized flexible bronchoscope that simultaneously operates a video camera and a convex ultrasound probe (which is installed at its distal end). Under real-time ultrasonographic visualization, the aspiration needle is inserted through the airway wall into the mediastinal target and the aspirate is sent for microbiologic or cytologic analyses as indicated (Fig. 286-2). Newer variants of this technique involve the use of core needles or mini-forceps, providing tissue specimens rather than aspirates that can be sent for histopathologic analysis. EBUS-TBNA has a sensitivity of approximately 90% for epithelial malignancies and approximately 70% for lymphoma (higher for detecting cases of lymphoma recurrence than for *de novo* lymphoma). For sarcoidosis, estimates point to a sensitivity of at least 80%

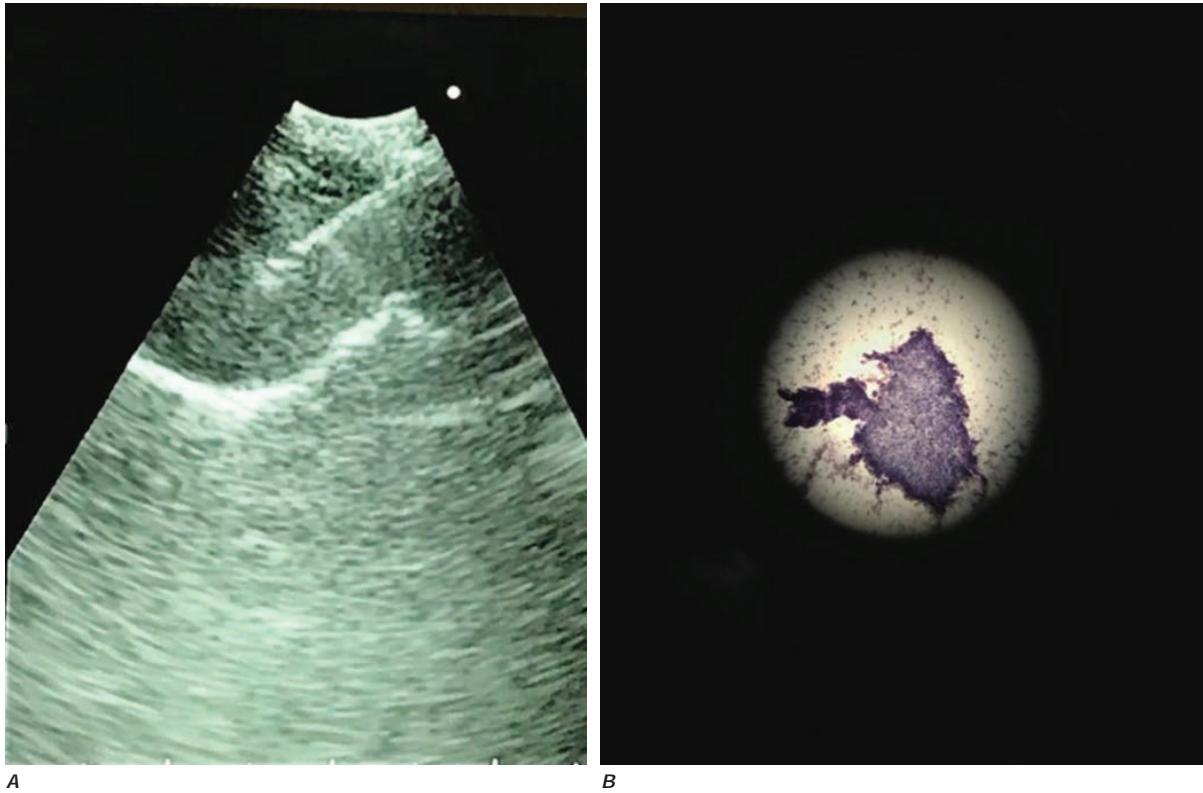


FIGURE 286-2 *A*. Endobronchial ultrasound-guided transbronchial needle aspiration of a mediastinal lymph node. *B*. Rapid on-site evaluation (ROSE) using Diff-Quik stain indicative of noncaseating granuloma. (Source: Majid Shafiq, MD, MPH)

2142 (higher if combined with endobronchial and transbronchial biopsies). EBUS-TBNA has been shown to provide adequate amounts of material to provide ancillary testing in cases of malignancy, such as immunostaining or genetic testing. A related needle-based technique, also using ultrasound guidance, involves sampling mediastinal structures through the esophagus, which can be a useful adjunct to EBUS-TBNA as it may provide better access to certain mediastinal lymph node stations. The combined sensitivity of these two techniques is slightly higher compared to either one alone. Esophageal sampling can be accomplished either by inserting the same EBUS bronchoscope through the esophagus or by using the standard endoscope used by gastroenterologists for endoscopic ultrasound (EUS).

At many centers, EBUS-TBNA is accompanied by rapid on-site cytologic evaluation (ROSE), wherein a portion of the aspirated specimen is immediately examined by a cytotechnologist or pathologist using rapid staining. This rapid assessment, while often inadequate for a definitive final diagnosis, can be helpful in establishing adequacy of sampled material by providing the bronchoscopist with real-time feedback on whether additional sampling is advisable.

The optimal way to process samples obtained via EBUS-TBNA is unknown. Some centers practice the tissue coagulum clot method, in which multiple aspirates are emptied onto a single piece of filter paper to form a clot that can help with preparation of a cell block. Other centers simply use the residue from spun specimens for this purpose. There is no conclusive evidence that one technique is superior to the other, but this question has not been well studied to date.

Guided Peripheral Bronchoscopy Guided peripheral bronchoscopy involves the use of advanced tools to aid with one or more of three tasks involved in successful bronchoscopic sampling of peripherally located lesions, such as lung nodules (see below). Various tools are available to help the bronchoscopist accomplish these tasks (Fig. 286-3).

(A) Navigating to the appropriate lobe/segment/subsegment: Electromagnetic navigational bronchoscopy (which involves GPS-like feedback as the bronchoscope is advanced toward the target) and virtual bronchoscopy (which overlays live endoscopic images onto a CT-derived virtual bronchoscopic map) can help with successful navigation through the airways. Shape-sensing technology, used

- as part of one robotic bronchoscopy platform (see below), also aims to achieve the same purpose.
- (B) The aforementioned technologies can also help localize a lesion, although they are limited by relying on previously acquired CT images that may or may not accurately represent precisely where the lesion is currently located in a three-dimensional space. Radial EBUS uses a thin ultrasound-tipped catheter that can be passed through the bronchoscope's working channel all the way to the lung periphery. This provides real-time images of structures beyond airway walls. A concentric image of the target, indicating a lesion with the airway going through its center, is associated with a high diagnostic yield. Alternatively, fluoroscopic imaging can be used to recalibrate the precise target location on navigational bronchoscopic platforms, potentially improving localization as well. Cone-beam CT, which is a distilled version of CT imaging that has been used intra-procedurally in multiple other fields such as interventional radiology, can be used for confirmation of optimal tool-in-lesion (with the patient undergoing a breath hold) prior to sampling.
- (C) The tools available for peripheral sampling include biopsy forceps, brushes, and aspiration needles as described above, with TBNA having the highest diagnostic sensitivity for discrete malignant lesions. Evidence for use of cryobiopsy for sampling discrete lesions in the lung periphery is currently limited. Recent innovations also include steerable sampling tools, which hold promise for more optimal sampling of the target lesion.

Robotic Bronchoscopy In 2018, the US Food and Drug Administration (FDA) approved two robotic bronchoscopy platforms for commercial use. These platforms offer improved bronchoscope stability and reach, but whether navigation, target localization, and adequacy of sampling are superior to other techniques is less certain. Early data on diagnostic yields are encouraging, but multicenter prospective data are not yet available.

MEDICAL IMAGING

Imaging has revolutionized the practice of medicine. Technologies such as x-ray, CT, MRI, and positron emission tomography (PET) can provide noninvasive assessments of alveolar perfusion, the metabolic

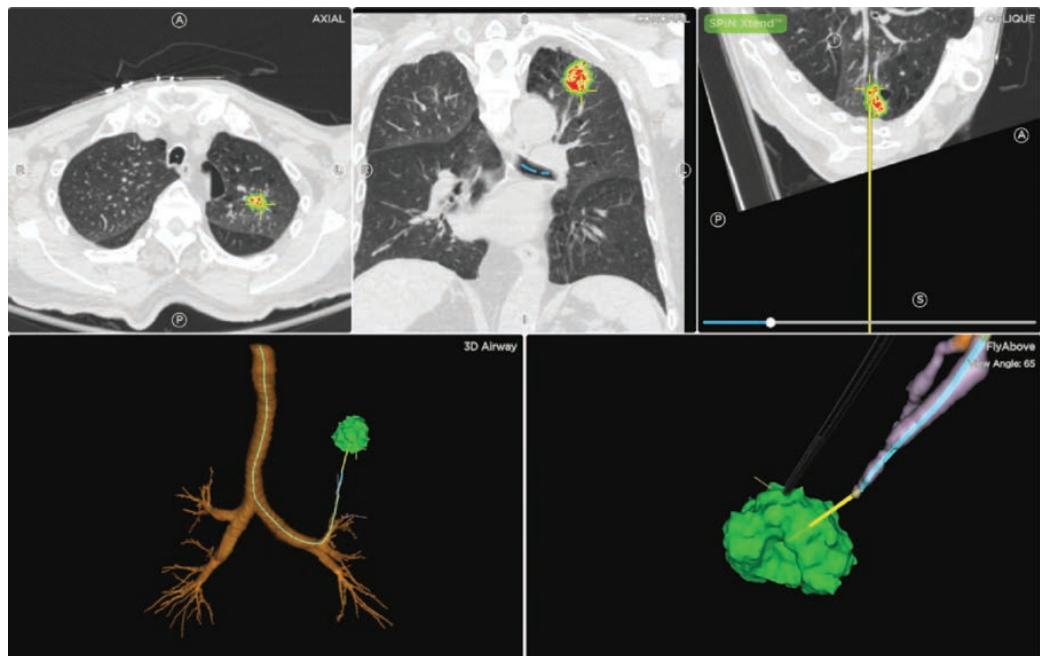


FIGURE 286-3 Example of an electromagnetic navigational bronchoscopic platform. The target lesion turns green when successfully reached by bronchoscopy. (Source: Majid Shafiq, MD, MPH)

activity of a lung nodule, the bronchovascular source of hemoptysis, or the earliest disease-related changes in parenchymal structure. Given the breadth of advances in respiratory system imaging and increasingly specialized applications across diseases, the following section is organized by technology. The final part of this section is dedicated to deep learning and the role it is increasingly playing in medical image interpretation.

CHEST X-RAY

The field of medical imaging can be traced back to work done by Wilhelm Roentgen in the 1890s. Roentgen noted that after connecting a cathode ray tube to a power supply, material in his lab would fluoresce even if the emission of visible light from the tube was blocked. He quickly deduced the presence of additional invisible “x-rays” and subsequently observed that their passage through solid material was attenuated in proportion to the material’s density. Within weeks of its discovery, x-ray technology was being widely leveraged to guide surgical exploration and the extraction of foreign objects such as shrapnel from the battlefield. Chest x-ray (CXR) has since become the foundation of clinical practice for respiratory medicine and is a widely available technology even in resource-limited settings.

The most commonly used CXR images for respiratory medicine are the posteroanterior (PA) and lateral films in the outpatient setting and anteroposterior (AP) films for those studies obtained at the bedside. These are 2-dimensional representations of 3-dimensional structures and the differing views can be used to examine superimposed structures (for example, a parenchymal opacity in the retrocardiac space). The contours of the chest wall, the silhouette of the heart, great vessels, and mediastinum, as well as the appearance of the parenchyma and bronchovascular bundle are all used to detect and classify disease as well as monitor its progression or response to therapeutic intervention. An example of a normal PA and lateral CXR is provided in Fig. 286-4.

In this image of the normal lung, many of the smaller structures such as the lymphatics and distal airways are beyond the ability of conventional x-ray technology to resolve. Larger structures such as the pulmonary vasculature may also be indistinct because of body position and the redistribution of blood flow to more gravitationally dependent regions. Diseases involving these structures may enhance or obscure their appearance. An example of these diseases is congestive heart failure where the lymphatics become engorged (Kerley B lines), the non-dependent vasculature more prominent (cephalization), and the outer

boundaries of the bronchial walls blurred (bronchial cuffing). Each of these findings must be clinically contextualized and while a thickened interstitium may be due to hydrostatic pulmonary edema, it may also be indicative of interstitial lung disease or carcinomatosis. CXR can also be used to discriminate pulmonary and extra-pulmonary disease and because of that it is an excellent initial diagnostic for nonspecific symptoms. An elevated hemidiaphragm, fibrosis of the mediastinum, or hyperlucency of the lung parenchyma all reflect processes that cause dyspnea, but their treatment and prognosis differ markedly.

COMPUTED TOMOGRAPHY

CT was introduced to clinical care in the 1980s and quickly became one of the most heavily leveraged modalities for medical imaging. While CXR provides one or two views of the thorax from which an experienced clinician must disambiguate overlying structures, CT provides spatially resolved reconstructions of all structures in the thorax. The acquisition of a CT scan involves the same basic process as an x-ray with a patient placed between a source of photons and a detector, but the image reconstruction and advanced analytics that can be applied to those images differ markedly. The passage of photons through the body is impeded in proportion to tissue density. This absorption or attenuation of photon passage is measured in Hounsfield units (HU) and clinical CT scanners are regularly calibrated to a standard scale with water having an HU of 0 and air -1000 HU. The broad range of tissue densities (reflected as attenuation values) in the thorax and the limited human ability to visually discriminate between two structures of similar densities are addressed by modifying the image display. A window width and level (the range and center of the range of HU values to display) is selected to optimize viewing structures of interest. For example, lung windows are optimized for visual inspection of the low-density lung parenchyma and all of the surrounding higher-density structures appear white, whereas the mediastinal windows are optimized to view the higher-density structures and anything of lower tissue density such as the lung parenchyma appears black. This does not change the HU values of the voxels (3-dimensional pixels) in the image, just their presentation for visual inspection.

The visual interpretation of thoracic CT is based upon the appearance of the secondary pulmonary lobule. This structure is a fundamental subunit of the lung consisting of a central airway and pulmonary artery, parenchyma, and then surrounding interstitium with the lymphatics and pulmonary veins (Fig. 286-5).

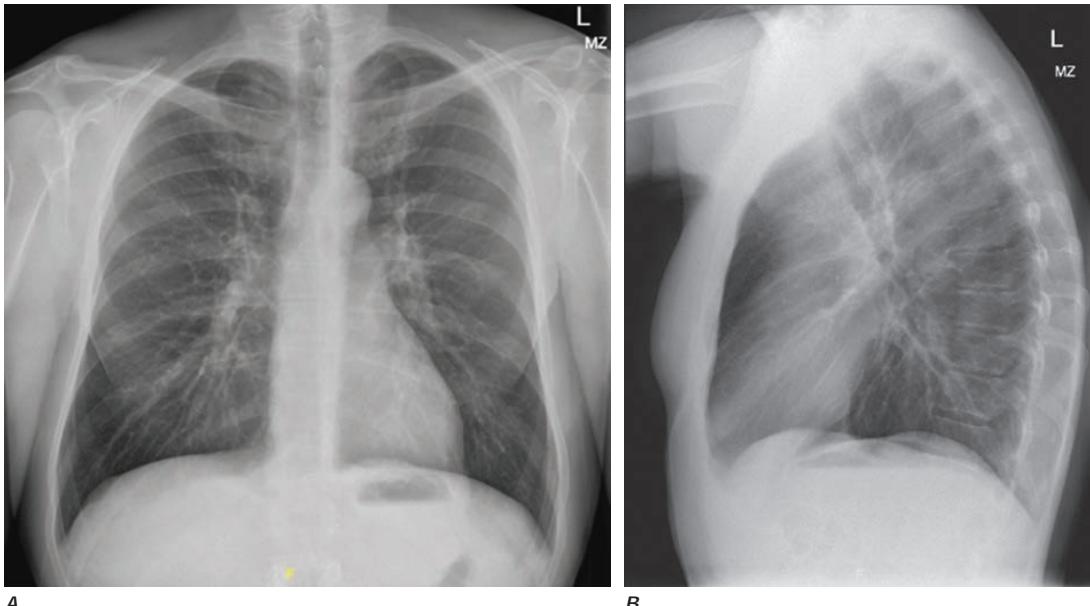


FIGURE 286-4 Posteroanterior (A) and lateral (B) CXR of a normal healthy subject. (Source: George Washko)

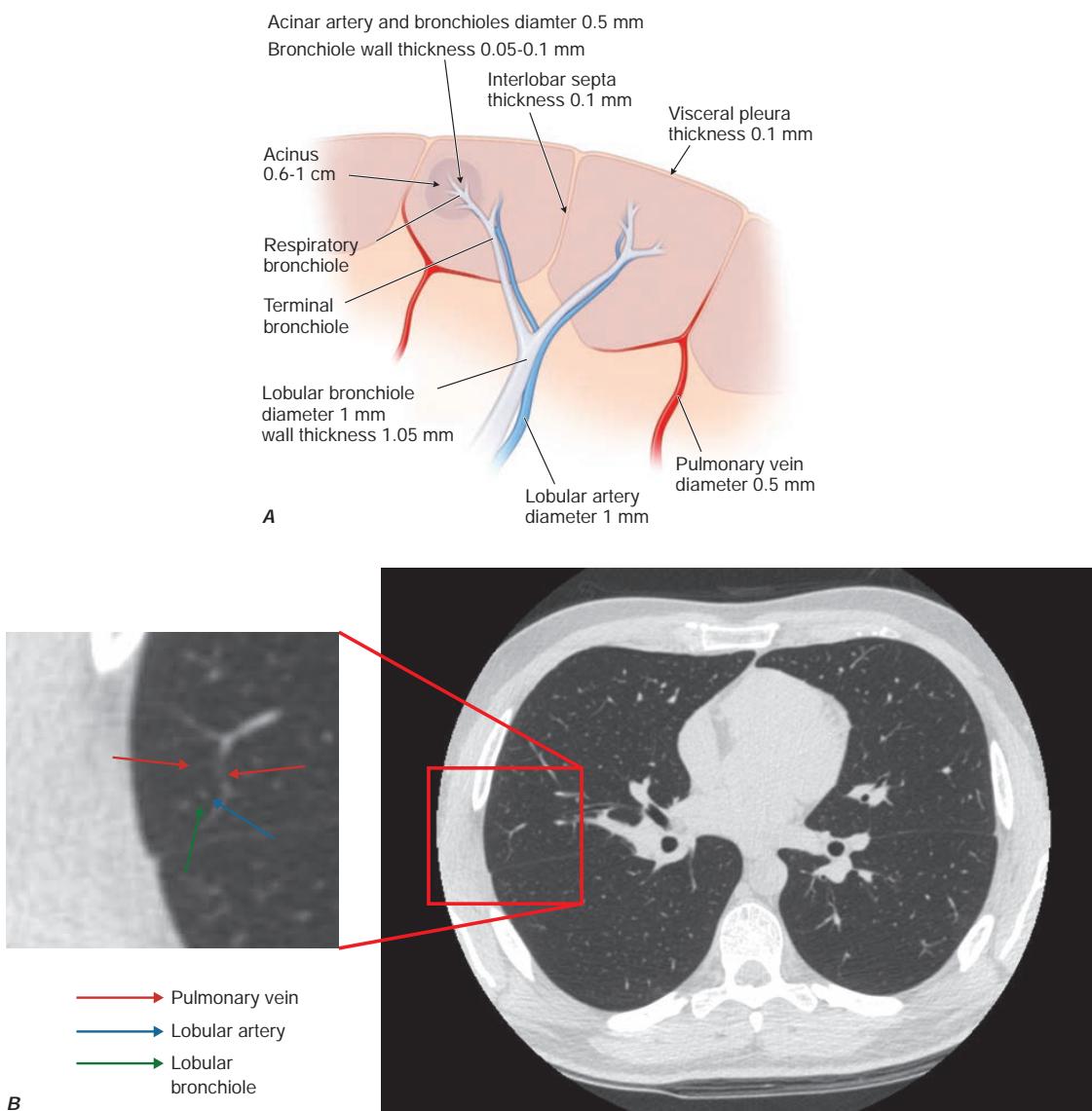


FIGURE 286-5 **A.** Illustration of the anatomy of the secondary pulmonary lobule. **B.** CT image showing the visible anatomy of the secondary pulmonary lobule. (Panel A adapted from WR Webb: Thin-section CT of the secondary pulmonary lobule: Anatomy and the Image—The 2004 Fleischner Lecture. Radiology 2006;239:322, 2004; Panel B source from Samuel Yoffe Ash MD)

Processes affecting the small airways such as respiratory bronchiitis may appear as centrilobular nodules. Parenchymal diseases such as emphysema may begin by effacing the centroid of the lobule (CLE: centrilobular emphysema), the periphery of the lobule (PSE: paraseptal emphysema), or diffusely across the lobule (PLE: panlobular emphysema). Pathology of the lymphatics or interstitium (interstitial lung disease, ILD) results in beading and/or thickening of the interlobular septa. **Examples of many of these processes are provided in Chaps. 292 and 293.**

The diagnostic information provided by the appearance of the secondary pulmonary lobule is further augmented by the distribution of these patterns of injury across the lung. Whereas CLE tends to first appear in the upper lung zones, PLE has a predilection to be basilar predominant. Interstitial thickening in the apices is more likely to be nonspecific interstitial pneumonitis (NSIP) while a basal and dependent predominant distribution of that same process is more consistent with idiopathic pulmonary fibrosis (IPF).

Finally, morphology of the central airways and vessels can be used to diagnose disease and estimate its severity. Bronchiectatic dilation of the

airways may be cylindrical and predominantly in the lower lobes as is seen in chronic obstructive pulmonary disease (COPD), cystic dilation in the upper lobes (cystic fibrosis), or there may be a focal nonspecific dilation of an airway due to prior infection. Pathologic dilation of the airways may also be due to disease of the surrounding parenchyma. Because of the mechanical interdependence of the bronchial tree and parenchyma, conditions that reduce lung compliance may result in traction bronchiectasis. This may be a local process or more diffuse depending on the distribution of the underlying parenchymal disease, and likely provides further insight into disease severity.

The caliber of the central pulmonary arterial (PA) trunk proximal to its first bifurcation is directly related to pulmonary arterial pressure. A measure of >3 cm is suggestive of the presence of elevated pulmonary vascular pressures and more recent studies have demonstrated that an increased ratio of the PA diameter to the diameter of the adjacent aorta (PA/A) provides a metric of disease severity and in the case of chronic respiratory diseases such as COPD is prognostic for both acute respiratory exacerbations and death. Assessment of the intraparenchymal pulmonary vasculature is typically augmented through the intravenous

infusion or bolus of iodinated contrast. This bolus and subsequent image acquisition may be timed to visualize passage of contrast through the pulmonary arteries to enable detection of thromboembolic disease, which appears as dark filling voids in otherwise bright white vessels.

It must be noted that the acquisition of CXRs and thoracic CT scans involves exposing the patient to ionizing radiation. Several studies have estimated the excess numbers of cancer due to CT scanning and extensive efforts have been made by both CT manufacturers and clinicians to reduce the radiation dose to the lowest possible amount that does not jeopardize image quality and interpretability.

MAGNETIC RESONANCE IMAGING

MRI is based upon the behavior of protons in a magnetic field. A strong magnetic field is applied to align the protons and then a pulse of radiofrequency current is then applied to the subject. This perturbs the protons and the speed at which they subsequently realign differs based upon the properties of the tissues within the region of interest. While this technique provides exquisite imaging data for the chest wall or solid organs such as the brain or heart, the abundance of air in the lung creates an artifact that impairs direct assessment of the parenchyma. For this reason, MRI of the lung leverages intravenous contrast agents such as gadolinium and is increasingly exploring the use of inhaled agents such as hyperpolarized noble gas. These respective agents enable *in vivo* assessments of organ perfusion and detailed measures of the morphology of the distal airspaces. An example of noble gas-enhanced MRI is shown in Fig. 286-6. The inhaled agent is ^3He and because it is proton rich, it can be used to examine lung ventilation visually and objectively. Regions of the lung that are poorly ventilated due to disease of the airways or distal airspaces have low concentrations of ^3He and appear as dark regions in an otherwise bright blue organ.

While an MRI may have a longer acquisition time than CT, and the geometry of the equipment often leads to a sense of claustrophobia, it does not involve the administration of ionizing radiation. This makes it a modality of choice in the pediatric population or clinical situations where repeated assessments are required.

POSITRON EMISSION TOMOGRAPHY

PET generates an image based upon the aggregation of radiolabeled tracers. The most common agent used for these purposes is $[^{18}\text{F}]\text{-fluoro-2-deoxyglucose}$ (FDG). This radiolabeled glucose analogue is administered intravenously and is taken up by cells in direct proportion to their metabolic activity. In the clinical setting, it is most commonly used for the discrimination of benign and malignant lung nodules, as well as lung cancer staging. Given the relatively low resolution of PET, co-registration with CT is common and the aligned imaging modalities allow the reader to determine the structural source of heightened metabolic activity.

There is increasing interest in the use of PET imaging in the biomedical community. These applications are largely still confined to research but advances in areas such as *in vivo* assessments of vascular biology in acute and chronic disease have been impressive.

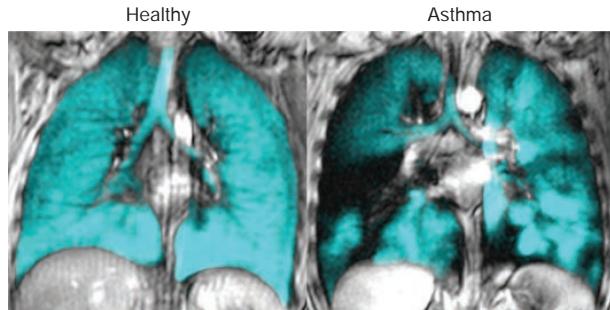


FIGURE 286-6 Noble gas MR. Healthy control on left and asthma on right. (Images courtesy of Grace Parraga, PhD, Department of Medical Biophysics, Department of Medicine, School of Biomedical Engineering, Robarts Research Institute, Western University, London, Ontario, Canada.)

ARTIFICIAL INTELLIGENCE/DEEP LEARNING

The final aspect to thoracic imaging that must be discussed is the growing field of artificial intelligence and deep learning applied to image analysis. Classic machine learning approaches to medical image interpretation involve the development of advanced algorithms to detect structures of interest, segment their boundaries, and then extract metrics related to size, shape, texture, etc. The massive increase in processing capacity afforded by graphical processing units (GPUs), the increasing availability of large amounts of data, and the wide dissemination of open-source software libraries allowing developers to create powerful work environments has led to explosive growth in the utilization of deep learning for image analytics. Some of the first medical applications of deep learning were in the field of dermatology and, more recently, this advanced form of pattern recognition has been reported to excel at the discrimination of benign and malignant lung nodules in thoracic CT scan. The breadth of application of these tools continues to expand to include image navigation and feature detection, biomarker development, and direct prediction of clinical outcomes. An example of deep learning-enabled segmentation of the heart and pulmonary vasculature from noncontrast enhanced noncardiac gated CT scan is shown in Fig. 286-7.

TRANSTHORACIC NEEDLE ASPIRATION

Radiologically guided needle biopsy has served as a long-standing mechanism for evaluation of parenchymal lung lesions, both malignant and infectious. In the setting of published guidelines recommending low-dose screening CT scan for lung malignancy in high-risk patients and with evolving guidelines for monitoring and assessment of incidental lung lesions arising in this setting, radiologically guided sampling of lung lesions has become an increasingly important mechanism to address parenchymal lung abnormalities concerning for cancer. Moreover, as novel immune modulators and biologic agents are increasingly utilized for the management of systemic disease and transplantation, effective interventions are becoming progressively more important in assessing for potential pulmonary infections arising as complications of immune suppression. Transthoracic needle aspiration (TTNA) remains one important arm in the assessment of these pulmonary complications.

TTNA can be accomplished with a variety of complementary imaging mechanisms, including under fluoroscopic, CT, ultrasound, or MRI guidance. CT is currently the most common imaging modality



FIGURE 286-7 Arterial/venous segmentation of the pulmonary vasculature (blue: arteries; red: veins) and epicardial surface of the right (blue) and left ventricles (red). (Image courtesy of Raul San Jose Estepar, PhD, Applied Chest Imaging Laboratory, Department of Radiology, Brigham and Women's Hospital, Boston, MA.)

2146 used to assess parenchymal lung lesions, with sensitivity and specificity reported to be >90%. Sensitivity of CT-guided TTNA is increased in more peripheral lesions. Transthoracic ultrasound has the advantages of a low complication rate in the setting of fine needle aspiration (FNA) and portability, allowing for more logistical simplicity in the setting of lung lesion assessment. In a prospective study of ultrasound-guided percutaneous FNA compared with CT-guided FNA, diagnostic rates were comparable between the two groups, with shorter procedure time associated with ultrasound guidance, numerical suggestion of decreased complication rate using ultrasound guidance, and lower costs associated with ultrasound guidance. Use of elastography to better characterize lung lesions has also been proposed in the context of ultrasound, though additional diagnostic yield has not yet been proven. Color Doppler ultrasonographic imaging has been demonstrated to have a high sensitivity and specificity and a low complication rate in another study. Electromagnetic guidance, unlike CT imaging, can be used in combination with endobronchial ultrasound and or navigational bronchoscopy in the operative setting, theoretically allowing for a multimodal approach that could increase diagnostic yield and allow for a combined staging procedure. Electromagnetic TTNA alone has demonstrated an 83% diagnostic yield in a pilot study, with an increase to 87% when combined with navigational bronchoscopy. Conflicting data are available regarding the diagnostic superiority of TTNA compared with alternative biopsy modalities such as endobronchial ultrasound for diagnosis of lung lesions, and results may depend on center experience.

Transthoracic sampling can be obtained using FNA or core needle biopsy. In one retrospective study, FNA was found to have an inferior diagnostic rate, compared with core needle sampling, as well as lower specificity. In this study, a method involving two FNA passes was compared to core needle sampling with six cores obtained from a single pass. No significant differences in complication rates were noted. In another retrospective study, in which procedure was determined by operator preferences, core needle aspirate samples were more likely to provide sufficient material for molecular testing than FNA. A systematic review of these techniques concluded that insufficient evidence was available to support a difference between FNA and core needle biopsy in diagnostic efficiency, though core needle biopsy may be more specific in diagnosing benign lung lesions. Given the negative predictive value estimate of 70%, negative results from TTNA are less reliable than positive results and should not be considered definitive to eliminate the concern for malignancy. Further assessment is needed to directly compare imaging modalities for TTNA guidance and to compare TTNA with other diagnostic modalities to determine the optimal choice of procedure in particular settings. Choice of procedure should be considered in the context of the size and location of the lesion, the experience of the center and operator, and patient-specific factors.

In regards to the safety of TTNA, in a retrospective study from 2015, the presence of mild to moderate pulmonary hypertension in patients did not increase complication rates in the setting of TTNA. The complication rates noted in this report were substantial, however, with hemorrhage occurring in one-third to one-quarter of patients, and pneumothorax in 17–28%. The majority of pneumothoraces did not require chest tube placement. Other complications included hemoptysis and hemothorax, though these were uncommon. These complication rates are consistent with those reported in other studies. In a meta-analysis of complication rates of CT-guided TTNA, complication rates were higher with core needle aspirates than FNA (38.8% [95% CI 34.3–43.5%] vs 24% [95% CI 18.2–30.8%]). The majority of these complications were minor. Risk factors for complications with FNA included smaller nodule diameter, larger needle diameter, and increased traversed lung parenchyma. No clear risk factors were noted for complications after core needle biopsies in this publication. More generally, the risks of TTNA increase for more centrally located lesions and those residing in close proximity to intrathoracic vasculature.

Despite the outstanding questions regarding the optimal approach for TTNA, this modality has been shown to be effective in cancer diagnosis in the thorax. Adenocarcinoma has become the most prevalent parenchymal lung malignancy in reported studies, and also the most

common malignant diagnosis found on TTNA of the lung. TTNA can also be effective in diagnosing less common tumors of the lung, both malignant and benign, including squamous and small cell carcinomas, lymphomas, and others, as well as in assessing tumors of the mediastinum. The diagnostic utility of TTNA is consistent across solid, subsolid, and partially calcified lung nodules. Immunocytochemistry markers can be utilized in TTNA samples to assist with diagnosis, prognosis, and prediction of response to therapy, and samples should be preserved whenever possible to allow for these studies, if needed. RNA extraction has also proven feasible in the setting of a single FNA sample, which could be instrumental in gene expression profiling, though this has thus far only been successfully accomplished in a research context.

The utility of TTNA in diagnosing pulmonary infections is variable in published literature. Some publications have reported that TTNA establishes a diagnosis of infection in 60–70% of cases, with a particularly high yield in the setting of Aspergillus infections. TTNA has also been shown to be particularly effective in the diagnosis of pulmonary tuberculosis, though a wide variety of infections have been diagnosed using this method. The presence of necrosis in lung lesions makes establishing an infectious diagnosis more likely using TTNA. Numerous staining techniques are available to assist with infectious diagnoses, and immunohistochemistry can also aid in the diagnosis of infection. Cytology should be correlated with histopathology and culture results, when available. Metagenomics using next-generation sequencing for detection of infection is evolving but requires further study. TTNA has also been useful in identifying granulomatous inflammation, which can provide supportive evidence of a granulomatous parenchymal lung disease in the appropriate clinical setting.

In summary, TTNA is an important element of diagnostic algorithms in the setting of lung nodules and masses, particularly when concern for malignancy is not high enough to warrant immediate excision, when the patient is not a surgical candidate, or the lesion or disease is not amenable to surgical resection. Further study is needed, however, to better understand the role of TTNA and other diagnostic modalities in the evaluation of parenchymal lung lesions.

MISCELLANEOUS TESTING

SPUTUM TESTING

Sputum microscopy and culture are commonly utilized to diagnose respiratory tract infections and identify the causative organisms. In patients with productive cough the sampling is simple and noninvasive, however, subject to patient technique and the potential for oropharyngeal and/or upper respiratory tract contamination. In those who are not expectorating, sputum induction can be considered using provocative nebulization with saline. Numerous studies have attempted to define criteria for reliability and reproducibility of sputum samples. The majority include quantification of number of epithelial cells and white blood cells per low power field, and many assess the ratio of the two for adequacy of sampling. None has been confirmed as superior in establishing the reliability of sampling to reflect lower respiratory tract growth. The quality of the sputum sample directly impacts the diagnostic reliability in the setting of bacterial pneumonia. Growth of *Mycobacterium tuberculosis*, *Legionella*, or *pneumocystis* should raise concern for infection, even in the setting of a poor sample. Endotracheal aspirates have not been demonstrated to be clearly superior to expectorated sputum in terms of diagnostic reliability, but such sampling may be required if spontaneous coughing is nonproductive and induced sputum is not feasible or successful.

As in the context of infection, sputum cytologic analysis has been utilized to assist in the diagnosis of malignancy, mainly because it can be obtained noninvasively. While sputum cytology demonstrating malignant cells is highly specific for a diagnosis of lung malignancy, its sensitivity has been reported at <40%. A systematic review of screening methods demonstrated no added benefit from sputum cytology when combined with CXR to screen for lung cancer. Advanced molecular techniques such as polymerase chain reaction, DNA methylation markers, micro-RNA assessment, and tumor-related protein analysis have

been proposed in sputum assessment for diagnostic purposes and risk stratification. At present, however, sputum cytology is recommended only when more invasive techniques cannot be pursued, such as in patients with prohibitive comorbidities or in resource-limited settings.

EXHALED BREATH CONDENSATE

Exhaled breath condensate includes gaseous, liquid, and water-soluble components, with numerous biomarker types and collection system varieties developed over time. Validation standards for many components are still being determined. Exhaled nitric oxide is the most highly validated of the biomarkers identified in exhaled breath condensate. The fraction of exhaled nitric oxide (FeNO) has been demonstrated in higher concentrations in exhaled breath condensate of patients with asthma than in healthy individuals, and has been shown in some studies to correlate with the presence of eosinophils in the sputum and blood and with response to inhaled corticosteroids, though data are conflicting. For example, in a systematic review and meta-analysis, FeNO elevation increased the odds of having asthma in both children above the age of 5 years and adults. In another systematic review of FeNO utilization in the management of adults with asthma, the assessment was helpful in the management of severe exacerbations but had no significant impact on overall exacerbations or inhaled corticosteroid use. Moreover, evidence suggests that tailoring of asthma therapy based on sputum eosinophil levels was effective in decreasing asthma exacerbations, but tailoring of therapy based on FeNO was not beneficial in improving outcomes, and insufficient evidence was observed to advocate the use of either sputum analysis or FeNO in clinical practice. FeNO has also been shown to be influenced by ethnicity, and appropriate reference standards for different ethnic groups have yet to be established. While FeNO has been proposed as a potential clinical guide to management, its use has not been incorporated into all guideline recommendations, and it has not been formally approved for clinical use.

SWEAT TESTING

Assessment of chloride concentration in sweat using pilocarpine iontophoresis, or sweat testing, remains a key element in the diagnostic framework of cystic fibrosis (CF). This method utilizes pilocarpine to stimulate sweat production. As patients with CF suffer from alterations to the sodium chloride ion channel, measurement of electrolytes in their secretions such as sweat reveals elevated chloride concentrations, amongst other abnormalities. This testing has been considered the gold standard in the diagnosis of CF due to its functional nature, its relative noninvasiveness, the establishment of validated standards for its performance, and its ability to discriminate between healthy individuals and those with CF at a chloride concentration of >60 mmol/L. The likelihood of a diagnosis of CF at a concentration of <40 mmol/L has been observed to be low, and an indeterminate range was defined as 40–59 mmol/L, which could be consistent with the disease if genetic and clinical manifestations were supportive.

While functional testing such as sweat chloride testing remains an essential component of diagnostic algorithms in CF, the evolution of genetic analysis has led to identification of an extensive array of genetic mutations associated with varied phenotypic impacts in this disease. In this context, the indeterminate range of chloride concentrations of 40–59 mmol/L on sweat test analysis was found to inadequately identify milder or more heterogeneous forms of the disease associated with newly identified genetic mutations. As a result, the Cystic Fibrosis Foundation provided updated guidance for the interpretation of sweat test results, with a decreased lower threshold to define an intermediate range of chloride concentration (changed from 40–50 mmol/L to 30–50 mmol/L), which could be consistent with the diagnosis of CF in the appropriate genetic and clinical context. In a subsequent analysis, utilization of the new guidance was found to enhance the probability of identifying patients with CF without increasing the false-positive diagnosis rate in the population. Sweat testing is a critical component of the CF diagnostic algorithm but should be interpreted in the context of clinical manifestations of disease and correlated with genetic testing in those suspected of the diagnosis.

ALLERGY TESTING

Allergy testing is often considered in the assessment of environmental exposures, including seasonal allergens, food allergens, and drug allergens. In the case of drug allergens in particular, drug reactions are often reported based on remote history and are often unconfirmed. The hesitancy to re-expose patients with an unconfirmed drug allergy can lead to limited options for treatment, to delay in treatment, and to utilization of treatments with more extended spectrum, potentially influencing the resistance patterns of these agents. Drug reactions can be mediated by IgE (immediate type reactions, type I), IgG or IgM (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (type IV).

Skin testing, including patch testing and/or delayed intradermal testing, is available to test exposure to particular allergens and determine reactivity. These tests have been shown to aid in clinical phenotyping of type I reactions and potentially in type IV reactions, though their role in type IV assessment remains more controversial. In the context of suspected type I reactions, patch testing is more cost effective and may be as effective as intradermal testing in identifying potential causative agents. The negative predictive value of intradermal skin testing in assessing for IgE-mediated drug allergies is high; however, the high sensitivity of this testing limits its specificity, and results must be interpreted in the context of the pretest probability and the clinical experience of the patient. Skin tests have also been demonstrated to assist in identifying the causative agent in type IV reactions and to assess cross-reactivity between structurally related drugs. Intradermal testing may be more sensitive than patch testing to assess for type IV drug reactions. Though some debate continues regarding a mandatory role for skin testing in the assessment of potential drug allergies, drug provocation testing or rechallenge is generally regarded as safe in low-risk individuals with history of urticaria or immediate rash, whereas skin testing has been proposed as a preliminary assessment in higher-risk individuals with a history of two or more reactions, angioedema, or anaphylaxis, prior to consideration of drug provocation testing.

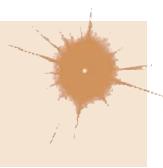
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Section 2 Diseases of the Respiratory System

287 Asthma

Elliot Israel



Asthma is a disease characterized by episodic airway obstruction and airway hyperresponsiveness usually accompanied by airway inflammation. In most cases, the airway obstruction is reversible, but in a subset of asthmatics, a component of the obstruction may become irreversible. In a large proportion of patients, the airway inflammation

2148 is eosinophilic, but some patients may present with differing types of airway inflammation, and in some cases, there is no obvious evidence of airway inflammation.

MANIFESTATIONS

Asthma most frequently presents as episodic shortness of breath, wheezing, and cough, which can occur in relation to triggers but may also occur spontaneously. These symptoms can occur in combination or separately. Other symptoms can include chest tightness and/or mucus production. These symptoms can resolve spontaneously or with therapy. In some patients, wheezing and/or dyspnea can be persistent. Episodes of acute bronchospasm, known as exacerbations, may be severe enough to require emergency medical care or hospitalization and may result in death.

EPIDEMIOLOGY

Asthma is the most common chronic disease associated with significant morbidity and mortality, with ~241 million people affected globally. Cross-sectional studies suggest that 7.9% of the population in the United States suffers from asthma as compared to ~4.3% prevalence worldwide. Prevalence continues to increase (starting at 7.3% in 2001 in the United States) and is associated with transition from rural to urban living. Asthma is more prevalent among children (8.4%) than adults (7.7%). In children, the prevalence is greatest among boys (2:1 male-to-female ratio), with a trend toward greater prevalence in women in adulthood. In some patients, asthma resolves as they enter adulthood only to "recur" later in life.

In the United States in 2016, 1.8 million people visited an emergency department for asthma, and 189,000 were hospitalized. The total economic cost in the United States in 2007 was estimated at \$56 billion. In the United States, asthma is more prevalent in blacks than Caucasians, and black race is associated with greater case morbidity. The ethnicity with the greatest prevalence in the United States is the Puerto Rican population.

Asthma mortality increased worldwide in the 1960s, apparently related to overuse of inhaled β_2 -agonists. Reduction in mortality since then has been attributed to increased use of inhaled corticosteroids. Asthma mortality declined globally from 0.44 per 100,000 people in 1993 to 0.19 in 2006, but further reduction in mortality has not occurred since that time.

TABLE 287-1 Exposures and Risk Factors Related to the Development of Asthma

1. Allergen exposure in those with a predisposition to atopy
2. Occupational exposure
3. Air pollution
4. Infections (viral and *Mycoplasma*)
5. Tobacco
6. Obesity
7. Diet
8. Fungi in allergic airway mycoses
9. Acute irritants and reactive airway dysfunction syndrome (RADS)
10. High-intensity exercise in elite athletes

THE PATHWAY TO THE DEVELOPMENT OF ASTHMA

The pathway to development of asthma can be varied. As illustrated in Fig. 287-1, there is an interplay between genetic susceptibility (see below) and environmental exposure and endogenous developmental factors (e.g., aging and menopause [see "Etiologic Mechanisms and Risk Factors" and Table 287-1]) that can lead to the development of asthma. Continued or additional exposures and triggers (Table 287-2) can affect the progression of disease and the degree of impairment.

PATOPHYSIOLOGY

MECHANISMS LEADING TO ACUTE AND CHRONIC AIRWAY OBSTRUCTION

The pathobiologic processes in the airways that lead to episodic and chronic airway obstruction of asthma are discussed below. Their pathologic correlates are highlighted in Fig. 287-2, illustrating the pathologic changes that can occur in asthmatic airways. These processes can occur individually or simultaneously. There can be temporal variation of these processes in an individual based on exogenous factors, discussed later in this chapter, as well as the aging process itself. These processes can involve the entire airway (but not the parenchyma), but there can be significant spatial heterogeneity, as has now been demonstrated using hyperpolarized gas ventilation studies and high-resolution computed tomography (CT) of the thorax.

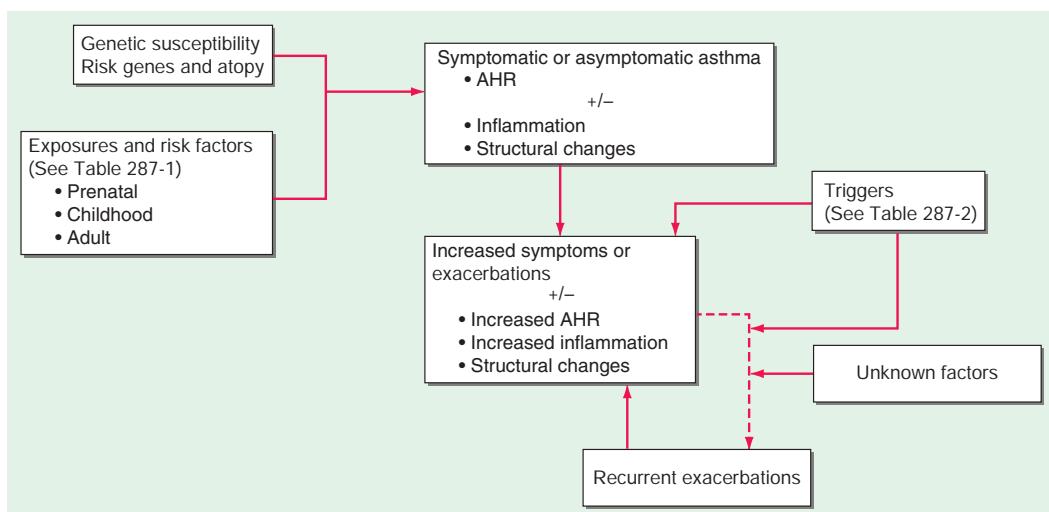


FIGURE 287-1 Asthma development pathway. Illustration of how genetic susceptibility and development and exposure during the life span interact to produce a disease that can vary in intensity and chronicity. Disease expression is characterized by airway hyperresponsiveness with varying degrees of airway inflammation and airway structural changes accompanied by varying degrees of symptoms that can be influenced by exposure to triggers that can cause acute deterioration as well as chronic symptoms. AHR, airway hyperresponsiveness.

TABLE 287-2 Triggers of Airway Narrowing

1. Allergens
2. Irritants
3. Viral infections
4. Exercise and cold, dry air
5. Air pollution
6. Drugs
7. Occupational exposures
8. Hormonal changes
9. Pregnancy

Airway Hyperresponsiveness Airway hyperresponsiveness is a hallmark of asthma. It is defined as an acute narrowing response of the airways in reaction to agents that do not elicit airway responses in non-affected individuals or an excess narrowing response to inhaled agents as compared to that which would occur in nonaffected individuals. A

component of the hyperresponsiveness occurs at the level of the airway smooth muscle itself as demonstrated by hyperresponsiveness to direct smooth-muscle-acting agents such as histamine or methacholine. In many patients, the apparent hyperresponsiveness is due to indirect activation of airway narrowing mechanisms as a result of stimulation of inflammatory cells (which release direct bronchoconstrictors and mediators that cause airway edema and/or mucus secretion) and/or stimulation of sensory nerves that can act on the smooth muscle or inflammatory cells. Agents and physical stimuli that elicit such responses are discussed later.

The apparent increased responsiveness of the airways in asthma may also have a structural etiology. In asthma, airway wall thickness is associated with disease severity and duration. This thickening, which may result from a combination of smooth-muscle hypertrophy and hyperplasia, subepithelial collagen deposition, airway edema, and mucosal inflammation, can result in a tendency for the airway to narrow disproportionately in response to stimuli that elicit increased airway muscle tension. A major therapeutic objective in asthma is to decrease the degree of airway hyperresponsiveness.

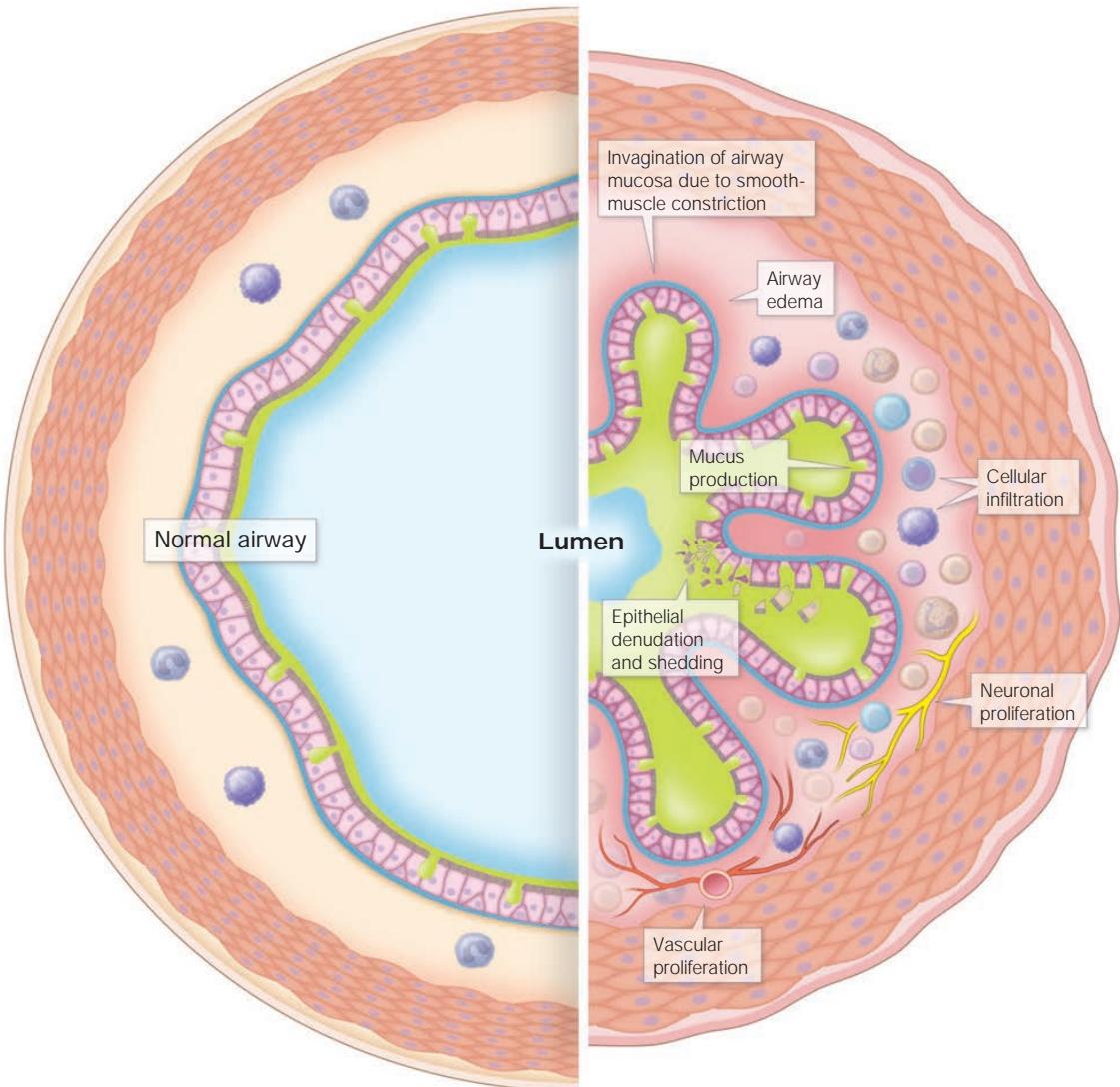


FIGURE 287-2 Pathologic changes that can be seen in asthmatic airways. Illustrated is a cross-sectional lumen of a bronchus. The left-hand side represents the normal airway, the right represents an asthmatic airway highlighting the pathologic changes that can be seen in asthma. The asthmatic airway lumen is reduced by smooth-muscle constriction, mucus in the airway lumen, and thickening of the submucosa due to edema and cellular infiltration. In addition, the ability of the lumen to increase in size with smooth-muscle relaxation may be impaired by deposition of collagen. The epithelium is disrupted, and there is evidence of vascular and neuronal proliferation. All these changes may not be present in one individual, and certain patients may have normal-appearing airways.

2150 Inflammatory Cells While airway inflammation can be precipitated by acute exposure to inhalants, most asthmatics have evidence of chronic inflammation in the airways. Most commonly, this inflammation is eosinophilic in nature. In some patients, neutrophilic inflammation may be predominant, especially in those with more severe asthma. Mast cells are also more frequent. Many inflammatory cells are present in an activated state, as will be discussed in the section on inflammation.

Airway Smooth Muscle Airway smooth muscle can contribute to asthma in three ways. First, it can be hyperresponsive to stimuli, as noted above. Second, hypertrophy and hyperplasia can lead to airway wall thickening with consequences for hyperresponsiveness, as noted above. Lastly, airway smooth-muscle cells can produce chemokines and cytokines that promote airway inflammation and promote the survival of inflammatory cells, particularly mast cells.

Subepithelial Collagen Deposition and Matrix Deposition Thickening of the subepithelial basement membrane occurs as a result of deposition of repair-type collagens and tenascin, periostin, fibronectin, and osteopontin primarily from myofibroblasts under the epithelium. The deposition of collagen and matrix stiffens the airway and can result in exaggerated responses to increased circumferential tension exerted by the smooth muscle. Such deposition can also narrow the airway lumen and decrease its ability to relax and thus can contribute to chronic airway obstruction.

Airway Epithelium Airway epithelium disruption takes the form of separation of columnar cells from the basal cells. The damaged epithelium is hypothesized to form a trophic unit with the underlying mesenchyme. This unit elaborates multiple growth factors thought to contribute to airway remodeling as well as multiple cytokines and mediators that promote asthmatic airway inflammation.

Vascular Proliferation In a subset of asthmatics, there is a significant degree of angiogenesis thought to be secondary to elaboration of angiogenic factors in the context of airway inflammation. Inflammatory mediators can result in leakage from postcapillary venules, which can contribute to the acute and chronic edema of the airways.

Airway Edema Submucosal edema can be present as an acute response in asthma and as a chronic contributor to airway wall thickening.

Epithelial Goblet Cell Metaplasia and Mucus Hypersecretion Chronic inflammation can result in the appearance and proliferation of mucus cells. Increased mucus production can reduce the effective airway luminal area. Mucus plugs can obstruct medium-size airways and can extend into the small airways.

Neuronal Proliferation Neurotrophins, which can lead to neuronal proliferation, are elaborated by smooth-muscle cells, epithelial cells, and inflammatory cells. Neuronal inputs can regulate smooth-muscle tone and mucus production, which may mediate acute bronchospasm and potentially chronically increased airway tone.

AIRWAY INFLAMMATION (TYPE 2 AND NON-TYPE 2 INFLAMMATION)

Most asthma is accompanied by airway inflammation. In the past, asthma had been divided into *atopic* and *nonatopic* (or *intrinsic*) asthma. The former was identified as relating to allergen sensitivity and exposure, with production of IgE, and occurring more commonly in children. The latter was identified as occurring in individuals with later onset asthma, with or without allergies, but frequently with eosinophilia. This paradigm is being superseded by a nosology that favors consideration of whether asthma is associated with type 2 or non-type 2 inflammation. This approach to immunologic classification is driven by a developing understanding of the underlying immune processes and by the development of therapeutic approaches that target type 2 inflammation (see later sections on asthma therapy).

Type 2 Inflammation Type 2 inflammation is an immune response involving the innate and adaptive arms of the immune system to promote barrier immunity on mucosal surfaces. It is called type

2 because it is associated with the type 2 subset of CD4+ T-helper cells, which produce the cytokines interleukin (IL) 4, IL-5, and IL-13. As shown in Fig. 287-3, these cytokines can have pleiotropic effects. IL-4 induces B-cell isotype switching to production of IgE. IgE, through its binding to basophils and mast cells, results in environmental sensitivity to allergens as a result of cross-linking of IgE on the surface of these mast cells and basophils. The products released from these cells include type 2 cytokines as well as direct activators of smooth-muscle constriction and edema. IL-5 has a critical role in regulating eosinophils. It controls formation, recruitment, and survival of these cells. IL-13 induces airway hyperresponsiveness, mucus hypersecretion, and goblet cell metaplasia. While allergen exposure in allergic individuals can elicit a cascade of activation of type 2 inflammation, it is now understood (see Fig. 287-3) that nonallergic stimuli can elicit production of type 2 cytokines, particularly due to stimulation of type 2 innate lymphoid cells (ILC2). These cells can produce IL-5 and IL-13. ILC2s can be activated by epithelial cytokines known as alarmins, which are produced in response to "nonallergic" epithelial exposures such as irritants, pollutants, oxidative agents, fungi, or viruses. Thus, these "nonallergic" stimuli can be associated with eosinophilia.

The development of anti-IL-5 drugs that dramatically reduce eosinophils has allowed us to determine that, in many asthmatics, eosinophils play a major role in asthma pathobiology. They may induce hyperresponsiveness through release of oxidative radicals and major basic protein, which can disrupt the epithelium. In addition, recent CT imaging has suggested that mucus plugs, which may contain significant amounts of eosinophil aggregates, may accumulate in the airways and contribute to asthma severity.

Non-Type 2 Processes As shown in Fig. 287-2, multiple processes can contribute to airway narrowing and apparent airway hyperresponsiveness. While type 2 inflammatory processes are most common, non-type 2 processes can exist either in combination with type 2 inflammation or without type 2 inflammation. Neutrophilic inflammation, as shown in Fig. 287-3, can also occur. This type of inflammation is more commonly seen in severe asthma that has not responded to the common anti-inflammatory therapies, such as corticosteroids, that usually suppress type 2 inflammation. In some cases, it may also be associated with chronic infection, occasionally with atypical pathogens such as *Mycoplasma*, perhaps accounting for the response of some of these patients to macrolide antibiotics. It is also commonly seen in reactive airway dysfunction syndrome (see "Etiologic Mechanisms and Risk Factors").

In a small subset of asthmatics, the pathologic changes seen in Fig. 287-2 may occur without any evidence of tissue infiltration by inflammatory cells. The etiology of such pauci-granulocytic asthma is unclear.

MEDIATORS

Many chemical substances or signaling factors can contribute to the pathobiologic picture of asthma. Some of them have been successfully targeted in developing asthma therapies.

Cytokines As illustrated in Fig. 287-3, and as discussed above, IL-4, IL-5, and IL-13 are the major cytokines associated with type 2 inflammation. They have all been targeted successfully in asthma therapies. Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 also play a role in the signaling cascade and are being actively studied as targets for treatment of asthma. IL-9 has been implicated as well. IL-6, IL-17, tumor necrosis factor (TNF- α), IL-1 β , and IL-8 have been implicated in non-type 2 inflammation.

Fatty Acid Mediators Proinflammatory mediators derived from arachidonic acid include leukotrienes and prostaglandins. The cysteinyl leukotrienes (leukotrienes C $_4$, D $_4$, and E $_1$) are produced by eosinophils and mast cells. They are potent smooth-muscle constrictors. They also stimulate mucus secretion, recruit allergic inflammatory cells, cause microvascular leakage, modulate cytokine production, and influence neural transmission. Cysteinyl leukotriene modifiers have shown clinical benefit in asthma. The non-cysteinyl leukotriene, LTB $_4$, is produced primarily from neutrophils but can also be synthesized

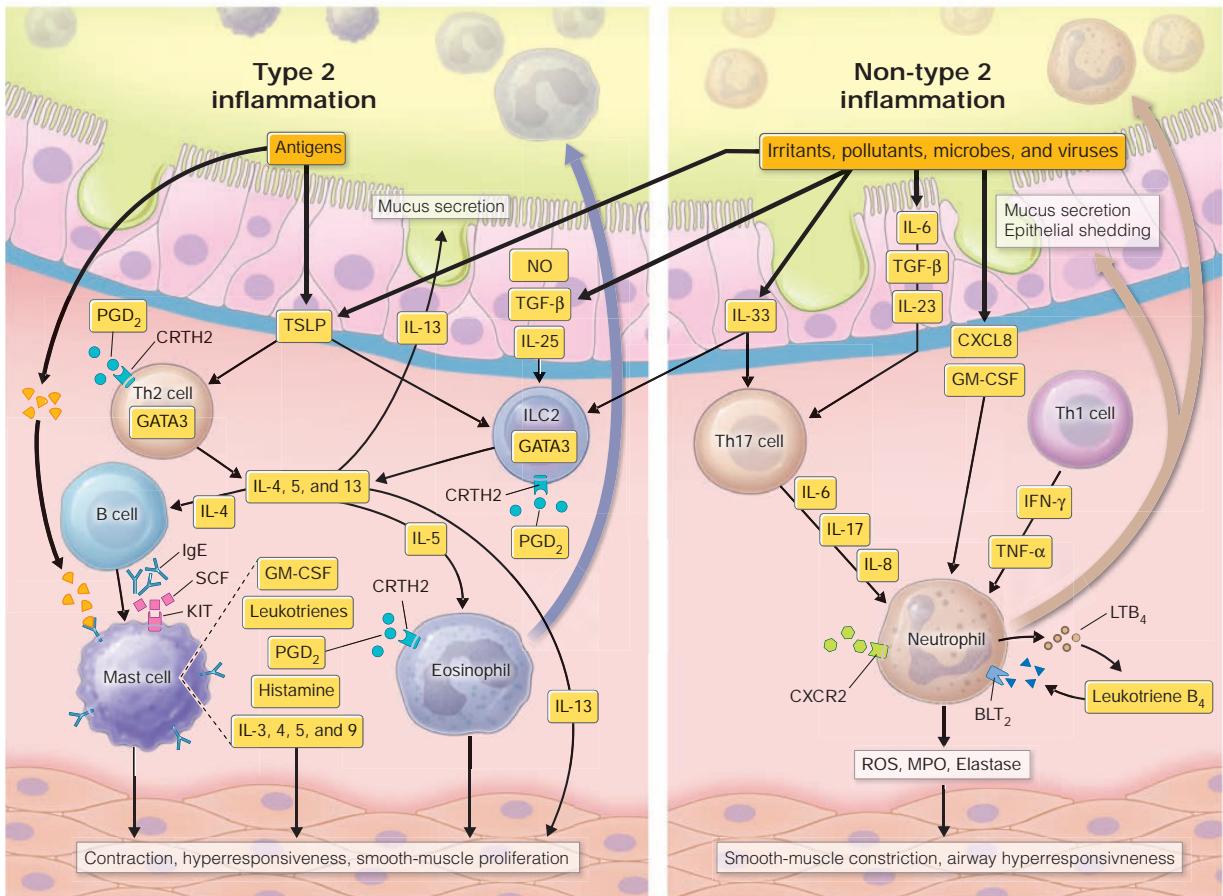


FIGURE 287-3 Inflammatory cells and mediators involved in type 2 and non-type 2 inflammation. Allergens and nonallergic stimuli can trigger activation of multiple inflammatory cells and release of mediators that are responsible for recruiting and activating these cells. The mediators can affect airway smooth-muscle proliferation and hyperresponsiveness and fibroblast proliferation and matrix deposition. BLT₂, leukotriene B₄ receptor 2; CRTH2, chemoattractant receptor-homologous molecule (PGD₂ receptor); CXCL8, CXC motif chemokine ligand 8; CXCR2, CXC chemokine receptor 2; GATA3, GATA Binding Protein 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon gamma; ILC2, innate lymphoid type 2 cells; KIT, mast/stem cell growth factor receptor; LTB₄, leukotriene B₄; MPO, myeloperoxidase; NO, nitric oxide; IL, interleukin; PGD₂, prostaglandin D₂; ROS, reactive oxygen species; SCF, stem cell factor; Th, T helper; TNF- α , tumor necrosis factor α ; TGF- β , transforming growth factor β ; T, Th helper; TSLP, thymic stromal lymphopoietin.

by macrophages and epithelial cells. It is a potent neutrophil chemoattractant. Prostaglandins are for the most part proinflammatory. Prostaglandin D₂ (PGD₂) is produced by mast cells. Receptors for PGD₂ (CRTH₂ receptors) are present on T_H2 cells, ILC2 cells, mast cells, eosinophils, macrophages, and epithelial cells, and the activation of these receptors upregulates type 2 inflammation. Initial studies with drugs blocking CRTH₂ have shown mild to moderate effectiveness in asthma.

There are several classes of fatty acid-derived mediators that are responsible for the resolution of inflammation. These include the resolvins and lipoxins. Several studies suggest that deficiencies in these moieties may be responsible for the ongoing inflammation in asthma, especially in severe asthma.

Nitric Oxide Nitric oxide is a potent vasodilator, and in vitro studies suggest that it can increase mucus production and smooth-muscle proliferation. It is produced by epithelial cells, especially in response to IL-13, and by stimulated inflammatory cells including eosinophils, mast cells, and neutrophils. Its precise role in the asthmatic diathesis is unclear. However, its production is increased in the airways in the presence of asthmatic eosinophilic inflammation, and it can be detected in exhaled breath.

Reactive Oxygen Species When allergens, pollutants, bacteria, and viruses activate inflammatory cells in the airway, they induce respiratory bursts that release reactive oxygen species that result in oxidative stress in the surrounding tissue. Increases in oxidative stress have been

shown to affect smooth-muscle contraction, increase mucus secretion, produce airway hyperresponsiveness, and result in epithelial shedding.

Chemokines A variety of chemokines are secreted by the epithelium (as well as other inflammatory cells) and attract inflammatory cells into the airways. Those of particular interest include eotaxin (an eosinophil chemoattractant), TARC and MDC (which attract T_H2 cells), and RANTES (which has pluripotent pro-phlogistic effects).

Etiologic Mechanisms, Risk Factors, Triggers, and Complicating Comorbidities

As illustrated in Fig. 287-1, the development of asthma involves an interplay between risk factors and exposures (see Table 287-1) and genetic predisposition.

HERITABLE PREDISPOSITION

Asthma has a strong genetic predisposition. Family and twin studies suggest a 25–80% degree of heritability. Genetic studies suggest complex polygenic inheritance complicated by interaction with environmental exposures. Further, epigenetic modifications related to environmental exposures may also produce heritable patterns of asthma. Many of the genes related to asthma have been associated with risk for atopy. However, there appear to be genetic modifications that predispose to asthma and its severity. Association studies have identified multiple candidate genes. In many cases, these genes vary from population

2152 to population. The most consistently identified include *ORMDL3*/GSDMB (in the 17q21 chromosomal region), *ADAM33*, *DPP-10*, *TSLP*, *IL-12*, *IL-33*, *ST2*, *HLA-DQB1*, *HLA-DQB2*, *TLR1*, and *IL6R*. In many cases, association studies have identified polymorphisms in noncoding regions of the genome, suggesting that the majority of the currently identified traits act as “enhancers” of biologic processes.

Genetic polymorphisms have also been associated with differential responses to asthma therapies. Variants in the β -receptor (Arg16Gly in *ADRB2*), the glucocorticoid-induced transcript 1 gene, and genes in the leukotriene synthesis and receptor pathways have been associated with altered response to the pharmacologic agents acting at those receptors or through those pathways.

While genetic variation plays a key role in asthma susceptibility, it is important to understand that unraveling the complexities of the genetic contribution to asthma remains elusive. To wit, only 2.5% of asthma risk can be explained by the 31 single nucleotide polymorphisms that have been associated with asthma.

A significant proportion of the heritability of asthma relates to the heritability of atopy. Atopy is the genetic tendency toward specific IgE production in response to allergen exposure. Serum levels of IgE correlate closely with the development of asthma. The National Health and Nutrition Examination Survey (NHANES) III found that half of asthma in patients aged 6–59 could be attributed to atopy with evidence of allergic sensitization. The allergens most associated with risk include house dust mites, indoor fungi, cockroaches, and indoor animals.

EXPOSURES AND RISK FACTORS

Allergic Sensitization and Allergen Exposure Like asthma, the development of allergic sensitization involves an interplay between heritable susceptibility and allergen exposure. Allergen exposure during vulnerable developmental periods is believed to increase the risk of development of allergic sensitization in those with a tendency toward atopy. Allergic sensitization is increased in industrialized nations. Recent research has suggested that varied microbiome exposure (exposure to bacteria and bacterial products) may influence the development of atopy with decreased risk for atopy in those in rural environments. Studies of the role of early allergen avoidance in reducing the risk of developing asthma have produced contradictory results, possibly related to the inability to eliminate all allergen exposure.

Tobacco Maternal smoking and secondhand smoke exposure are associated with increased childhood asthma. Childhood secondhand smoke exposure increased asthma risk twofold. Active smoking is estimated to increase the incidence of asthma by up to fourfold in adolescents and young adults.

Air Pollution Early life exposure to pollution increases the risk of development of asthma. Proximity to major roadways increases the risk of early childhood asthma, thought to be attributed to levels of nitrogen dioxide exposure. Decreasing nitrogen dioxide exposure has been found to decrease asthma incidence in children. Studies of exposure to mixed pollutants suggest that most risk lies with carbon monoxide and nitric dioxide, with marginal effects of sulfur dioxide. Indoor air pollution from open fires and use of gas stoves has been associated with increased risk of children developing asthma symptoms. Mechanistically, pollutants are thought to cause oxidative injury to the airways, producing airway inflammation and leading to remodeling and increased risk of airway sensitization.

Infections Respiratory infections clearly can precipitate asthma deteriorations. However, the degree to which respiratory infections indicate susceptibility to asthma, represent a causal factor, or in some cases provide protection from asthma is unclear. Incidence and frequency of human rhinovirus and respiratory syncytial virus infections in children are associated with development of asthma, but whether they play a causal role is unclear. Evidence of prior *Mycoplasma pneumoniae* infection has been associated with the development of asthma in Taiwanese adults.

Occupational Exposures Occupational asthma is estimated to account for 10–25% of adult-onset asthma. The occupations associated with the most cases in European Community Health Surveys were nursing and cleaning. Two types of exposures are recognized: (1) an immunologic stimulus (further subdivided into high-molecular-weight [e.g., proteins, flour] and low-molecular-weight [e.g., formaldehyde, diisocyanate] stimuli based on whether they act as haptens or can directly stimulate a response), and (2) an irritative stimulus. The immunologic form is associated with a latency period between time of exposure and development of symptoms. The irritative form, known as reactive airway dysfunction syndrome (RADS), will be discussed below. A combination of genetic predisposition (including atopy), timing, intensity of exposure, and co-exposure (e.g., smoking) influences whether an individual will develop occupational asthma.

Diet There are suggestions that prenatal diet or vitamin deficiency may alter the risk of developing asthma. The evidence is not yet definitive, but vitamin D insufficiency may increase asthma risk in the progeny and supplementation may decrease such risk. Similarly, preliminary studies suggest that maternal supplementation with vitamins C and E and zinc may decrease asthma in children. One study suggested that maternal polyunsaturated fatty acid supplementation may decrease childhood asthma risk. Observational studies have suggested that increased maternal sugar intake may increase childhood asthma risk.

Obesity Multiple studies suggest that obesity may be a risk factor for development of childhood and adult asthma. Adipokines and IL-6 have been thought to play a pathobiologic role. Some have argued that the risk is overestimated, and a study from NHANES II found an association with dyspnea but not with airway obstruction.

Medications There are conflicting data regarding prenatal and early childhood risk for asthma posed by certain classes of medications. Use of H₂ blockers and proton pump inhibitors in pregnancy has been associated with an increased risk of asthma in children (relative risk, 1.36–1.45); however, another study found a small risk for H₂ blockers only. Conflicting data have been presented on the risk of perinatal acetaminophen and early childhood acetaminophen use. In a prospective study, the use of acetaminophen was not associated with an increased risk of exacerbations in young children with asthma, when compared to ibuprofen.

Prenatal and Perinatal Risk Factors Preeclampsia and prematurity have been associated with increased risk of asthma in the progeny. Babies born by cesarean section are at higher risk for asthma. Those with neonatal jaundice are also at increased risk. Breast-feeding reduced early wheezing but has a less clear effect on later incidence of asthma.

Endogenous Developmental Risk Factors Asthma is more prevalent among boys than girls, with the difference receding by age 20 and reversing (more prevalent among women) by age 40. Atopy is more prevalent among boys in childhood, and they have reduced airway size compared with girls. Both factors are thought to contribute to the sex discrepancy. A subset of women develop asthma around menopause. Such asthma tends to involve non-type 2 mechanisms. Pregnancy may precipitate or aggravate asthma as well.

High-Concentration Irritant Exposure and RADS A solitary exposure to a high concentration of irritant agents that rapidly (usually within hours) produces bronchospasm and bronchial hyperactivity is known as RADS. Causative agents include oxidizing and reducing agents in an aerosol or high levels of particulates. The acute pathology usually involves epithelial injury with neutrophilia. There is little evidence of type 2 inflammation. This syndrome differs from occupational asthma in that these patients have not become sensitized to the provocative agent and can return to work in that environment once they have recovered. However, the course of the disease may be variable, with some series showing documented abnormalities and persistent symptoms 10 years after exposure.

Fungi and Allergic Airway Mycoses One to 2% of patients with asthma may have an IgE-mediated sensitization to colonization of the airway by fungi, with the most common fungus causing such a reaction being *Aspergillus fumigatus*. So-called allergic bronchopulmonary aspergillosis (ABPA) is characterized by a type 2 airway inflammatory response to aspergillus with IgE >1000 IU/mL, eosinophils >500/ μ L, positive skin test to *Aspergillus*, and specific IgE and IgG antibodies to *Aspergillus*. Patients may have intermittent mucus plugging and central bronchiectasis. Up to two-thirds of patients will grow *Aspergillus* from the sputum. Treatment involves systemic antifungal treatment with itraconazole or voriconazole and oral corticosteroids.

Exercise-Induced Symptoms in Elite Athletes Exercise-induced airway narrowing in elite athletes undertaking extreme exercise in strenuous condition. These athletes may have little, or no, airway hyperreactivity or asthma risk factors. The condition may involve additional mechanisms including direct epithelial injury. Such a syndrome has also been reported in swimmers possibly related to pool chlorination.

TRIGGERS OF AIRWAY NARROWING

The risk factors and exposures reviewed above lead to increased airway reactivity and a propensity to react to factors that trigger airway narrowing (see Fig. 287-1). Almost all asthmatics can identify triggers that will make their asthma worse. These triggers are listed in Table 287-2. Many of them overlap with the risk factors and etiologic factors reviewed above. In some cases, elimination of these triggers may dramatically reduce the impairment caused by asthma. In a minority, abatement can lead to “remission” so that these patients no longer require asthma medications and do not experience bronchospasm with their daily activities and routines. While acute exposures to these triggers generally cause short-lived bronchospasm, the bronchospasm may be severe enough that treatment for an exacerbation is required. Chronic exposure may lead to permanent deterioration in asthma control, although this does not appear to be true for exercise or stress. It should be noted that evidence suggests that severe asthma exacerbations (those requiring systemic corticosteroids) may, in and of themselves, accelerate lung function decline.

Allergens In patients with sensitization to particular allergens through production of allergen-specific IgE, exposure to those allergens by inhalation can result in activation of mast cells and basophils with acute production of bronchoactive mediators (see Fig. 287-3). Such exposure can produce immediate bronchospasm (early response) and a late response (2–24 h after exposure) with bronchial narrowing and inflammation. These mechanisms can account for reactions to inhalation of pollens, mold, or dust; insects (especially cockroaches); animals; occupational materials; seasonal worsening of asthma; and so-called “thunderstorm asthma.” Chronic exposure may lead to persistent symptoms. While food allergies can produce bronchospasm through anaphylaxis, food allergies are generally not etiologically linked to asthma.

Irritants Many asthmatics report increased symptoms on exposure to strong odors, smoke, combustion products, cleaning fluids, or perfumes. In general, the effects are short-lived, although chronic exposure (see “Occupational Exposures” above) and large-quantity exposures (see discussion of RADS above) can lead to long-lasting or permanent symptoms.

Viral Infections Most asthmatics report that asthma exacerbations can be triggered by upper respiratory infections. The inflammation that occurs may be neutrophilic as well as eosinophilic. There is some evidence that IgE generation may reduce production of interferon, possibly predisposing to the effects of upper respiratory viruses. Increased airway reactivity after viral infections generally persists for 4–6 weeks but, in some cases, may be associated with permanent changes and impairment.

Exercise and Cold/Dry Air Exercise may be a trigger to asthmatic bronchoconstriction in patients with asthma. Hyperventilation

that occurs with exercise dries the airway lining, changing the tonicity of lining cells and causing release of bronchoconstrictive mediators. This effect is more prominent the lower the moisture content of the air, and since cold air has a lower absolute moisture content, the lower the temperature of the inspired air, the less exercise is required to induce bronchoconstriction. In addition, cold air may produce airway edema during airway wall rewarming. At routine levels of exercise, these effects are short-lived.

Air Pollution Increased rates of exacerbations have been associated with increased ambient ozone, sulfur dioxide, and nitrogen dioxide, among other air pollutants.

Drugs Beta blockers may trigger bronchospasm even when used solely in ophthalmic preparations. While the more selective beta blockers are safe for most asthmatics, beta blocker use may be a cause of difficult-to-control asthma. Aspirin may precipitate bronchospasm in those with aspirin-exacerbated respiratory disease (see “Special Considerations”). Angiotensin-converting enzyme (ACE) inhibitors (and to a lesser extent angiotensin receptor blockers) may cause cough.

Occupational Exposures In addition to RADS (see above), episodic and/or recurrent exposures to workplace irritants and/or substances to which one has become sensitized can produce symptoms. These symptoms are usually reduced when patients are away from such exposures on weekends or vacation.

Stress Asthmatics may report increased symptoms with stress. The mechanisms are poorly understood.

Hormonal Factors A small proportion of women report a regular increase in perimenstrual symptoms, and symptoms may worsen during perimenopause. This may be related to rapid fluctuations in estrogen levels. Pregnancy can precipitate worsening of asthma in approximately one-third of pregnant patients.

COMORBIDITIES

Comorbidities may make asthma difficult to manage, and the common comorbidities are listed in Table 287-3.

Obesity Obese adults with asthma have more severe asthma symptoms than lean adults and are two to four times more likely to be hospitalized with an asthma exacerbation. Nonrandomized studies have shown an improvement and significant reduction in exacerbations after bariatric surgery.

TABLE 287-3 Differential Diagnosis and Comorbidities That May Make Asthma Difficult to Control

Differential Diagnosis of Diseases with Overlapping Symptoms That Can Present with Obstructive Pulmonary Function Tests

1. Heart failure
2. Chronic obstructive pulmonary disease (COPD)
3. α_1 antitrypsin deficiency
4. Airway obstruction from mass or foreign body
5. Inducible laryngeal dysfunction (vocal cord dysfunction)
6. Bronchiolitis obliterans
7. Bronchiectasis
8. Tracheobronchomalacia

Comorbidities That Can Make Asthma Difficult to Control

1. Chronic rhinosinusitis +/- nasal polypsis
2. Obesity
3. Gastroesophageal reflux disease
4. Inducible laryngeal dysfunction (vocal cord dysfunction)
5. COPD
6. Anxiety/depression
7. Obstructive sleep apnea

2154 Gastroesophageal Reflux Disease The presence of gastroesophageal reflux disease (GERD) predicts poor quality of life and is an independent predictor of asthma exacerbations. Treatment of symptomatic reflux disease has been shown to produce modest improvements in airway function, symptoms, and exacerbation frequency. Treatment of asymptomatic patients has not shown a benefit.

Rhinosinusitis And/Or Nasal Polypsis Rhinosinusitis may be a manifestation of the eosinophilic inflammation in the lower airway in asthma. In addition, poorly controlled rhinosinusitis is believed to aggravate asthma by several potential mechanisms including inflammatory and irritant effects of the secretions on the lower airway, neural reflexes, and production of inflammatory mediators and cells that produce systemic inflammation. Treatment with intranasal corticosteroids has been shown to decrease airway reactivity and emergency department visits and hospitalizations. Evidence for the benefit of surgical therapy is inconclusive. There is increasing evidence that biologics targeted at type 2 inflammation may also be particularly useful for asthma associated with rhinosinusitis and polypsis in particular.

Nasal polypsis is rare in children, and its presence in adults with asthma should raise suspicions of aspirin-exacerbated respiratory disease (see "Special Considerations").

Vocal Cord Dysfunction Now known as inducible laryngeal obstruction, vocal cord dysfunction involves inappropriate narrowing of the larynx, producing resistance to airflow. It can complicate asthma and mimic it. It is more commonly seen in women and patients with anxiety and depression. Definitive diagnosis involves laryngoscopy during symptomatic episodes or during induced obstruction.

Chronic Obstructive Pulmonary Disease (COPD) See "Asthma-COPD Overlap" under "Special Considerations."

Anxiety/Depression Increased rates of asthma exacerbations occur in asthmatics with anxiety, depression, or chronic stress. Some patients may be unable to distinguish anxiety attacks from asthma.

DIAGNOSIS AND EVALUATION

APPROACH

A presumptive diagnosis of asthma can usually be made based on a compatible history of recurrent wheezing, shortness of breath, chest tightness, or cough related to common bronchoconstrictor precipitants when appropriate components of the differential diagnosis have been considered and/or eliminated. In some cases, a therapeutic trial of low-dose inhaled corticosteroid (ICS) may be considered. In all but the mildest cases, the diagnosis should be confirmed with pulmonary function testing or demonstration of airway hyperresponsiveness. Unfortunately, the diagnosis may be difficult to confirm after initiation of therapy since airway obstruction and hyperresponsiveness may be mitigated with therapy. A trial of tapering medications may be necessary. Studies have shown that more than one-third of patients with a physician diagnosis of asthma do not meet the criteria for the diagnosis.

Adjunctive evaluation, as outlined below, should be undertaken to identify precipitating factors and underlying mechanisms that may be amenable to specific therapies (e.g., allergen avoidance). Cases that require more than a daily moderate-dose ICS combined with a long-acting β_2 -agonist (LABA) (together known as ICS/LABA) should undergo more formal evaluation to assess comorbidities that may make asthma difficult to control and a reassessment of any possible confounding diagnoses that may mimic asthma symptoms (see Table 287-3).

PRIMARY ASSESSMENT TOOLS FOR ESTABLISHING A DIAGNOSIS

History Patients with asthma most commonly complain of episodes of wheezing, shortness of breath, chest tightness, mucus production, or cough upon exposure to triggers listed in Table 287-2. Symptoms may be worse on arising in the morning. Some may have nocturnal symptoms alone. However, such patients should be evaluated for postnasal drip or GERD if that is their sole presenting

symptom. Patients frequently complain of symptoms with rapid changes of temperature or humidity. Exercise-induced symptoms are common with increased sensitivity to cold air. As compared to cardiac sources of dyspnea, exercise symptoms tend to develop more slowly after initiation of exercise and tend to resolve more slowly unless a β_2 -agonist is administered after the onset of symptoms. A careful exposure history should be obtained for home (e.g., pets, molds, dust, direct or secondhand smoke), work (work environment and exposure to occupational sensitizers), and recreational (e.g., hobbies, recreational inhalants) exposures. Allergen-sensitized patients may complain of symptoms on exposure to known allergens such as animals and may complain of increased symptoms during specific pollen seasons. Up to two-thirds of patients with asthma will be atopic (as opposed to half of the U.S. population), and almost half will have a history of rhinitis, with many complaining of intermittent sinusitis. In patients with adult-onset asthma, a careful occupational history should be obtained and a history of reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) or use of new medications, such as beta blockers (including ophthalmic preparations) and ACE inhibitors (due to potential cough), should be elicited.

Physical Examination In between acute attacks, physical findings may be normal. Many patients will have evidence of allergic rhinitis with pale nasal mucus membranes. Five percent or more of patients may have nasal polyps, with increased frequency in those with more severe asthma and aspirin-exacerbated respiratory disease. Some patients will have wheezing on expiration (less so on inspiration). During an acute asthma attack, patients present with tachypnea and tachycardia, and use of accessory muscles can be observed. Wheezing, with a prolonged expiratory phase, is common during attacks, but as the severity of airway obstruction progresses, the chest may become "silent" with loss of breath sounds.

Pulmonary Function Tests Effective reduction of the airway lumen in asthma produces increased resistance to airflow, which can be detected as a reduction in expiratory airflow during forced expiratory maneuvers. The peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV₁), and the FEV₁/forced vital capacity (FVC) ratio are reduced below the lower limit of normal. The flow-volume loop may show a characteristic scalloping (see Chap. 286). These findings may not be present during acute attacks or on therapy (especially after recent use of bronchodilators). Reversibility is defined as a $\geq 12\%$ increase in the FEV₁ and an absolute increase of ≥ 200 mL at least 15 min after administration of a β_2 -agonist or after several weeks of corticosteroid therapy. Diurnal peak flow variability of $>20\%$ has also been proposed as an indicator of reversible airways disease, but it is less reliable due to difficulties with quality control and variability of home assessments. Lung volumes and diffusing capacity should be normal in uncomplicated asthma.

Assessment of Airway Responsiveness In cases where pulmonary function tests are nonconfirmatory and the diagnosis remains in doubt, testing to demonstrate increased reactivity to provocative stimuli in the laboratory can be undertaken. Methacholine, a cholinergic agonist, inhaled in increasing concentrations is most commonly used. A provocative dose producing a 20% drop in FEV₁ (PD_{20}) is calculated, with a value ≤ 400 μ g indicative of airway reactivity. Mannitol is used as well, and occasionally, hypertonic saline may be used. Challenge with exercise and/or cold, dry air can be performed, with a positive response recorded if there is a $\geq 10\%$ drop in FEV₁ from baseline. In the case of suspected environmental/occupational exposures, specific allergen challenges may be undertaken in highly specialized labs.

ADJUNCTIVE ASSESSMENT TOOLS

Eosinophil Counts A large proportion of asthma patients not treated with oral or high-dose ICSs will have eosinophil counts >300 cells/ μ L. Eosinophil counts correlate with severity of disease in population studies. Their presence in patients with severe asthma indicates a likelihood that the patient would respond to medications

targeted at type 2 inflammation. Extremely elevated levels should prompt consideration of eosinophilic granulomatosis with polyangiitis or primary eosinophilic disorders.

IgE, Skin Tests, and Radioallergosorbent Tests Total serum IgE levels are useful in considering whether patients with severe asthma would be eligible for anti-IgE therapy. Levels >1000 IU/mL should prompt consideration of ABPA. Skin tests, or their in vitro counterparts that detect IgE directed at specific antigens (radioallergosorbent test [RAST]), can be useful in confirming atopy and suggesting allergic rhinitis, which can complicate asthma management. Allergy investigations may be useful, when correlated with a history of reactions, in identifying environmental exposures that may be aggravating asthma.

Exhaled Nitric Oxide Fraction of exhaled nitric oxide (FeNO) in exhaled breath is an approximate indicator of eosinophilic inflammation in the airways. It is easily suppressed by ICSs and, thus, can be used to assess adherence in patients in whom it was initially elevated. Elevated levels (>35–40 ppb) in untreated patients are indicative of eosinophilic inflammation. Levels >20–25 ppb in patients with severe asthma on moderate- to high-dose ICS indicate either poor adherence or persistent type 2 inflammation despite therapy.

ADDITIONAL EVALUATION IN SEVERE/POORLY RESPONSIVE ASTHMA

In patients with poorly responsive asthma, additional evaluations for comorbidities (see Table 287-3) may be necessary, including sinus radiographic studies (even in those who have no symptoms of sinus disease) and esophageal studies in those who have symptoms of reflux. In patients with nonreversible disease, many obtain a serum antitrypsin level. Additionally, the following evaluations may be of utility in poorly responsive asthma.

Chest Radiography Chest CT can be useful to assess for the presence of bronchiectasis and other structural abnormalities that could produce airway obstruction. New image analysis tools are being used in the research setting to assess airway properties such as airway wall thickness, airway diameter, and evidence of air trapping.

Sputum Induced sputum may be used in more specialized centers to help characterize type 2 and non-type 2 inflammation by detection of eosinophils and neutrophils, respectively. In severe asthma, there is some evidence that some patients may have localized persistent eosinophilic airway inflammation despite lack of peripheral eosinophils on blood analysis.

TREATMENT

Asthma

GOALS OF ASTHMA THERAPY AND ASSESSMENT OF CONTROL

Goals of asthma therapy in terms of achieving control of symptoms and reducing risk (as reflected in frequency of asthma exacerbations) are listed in Table 287-4. The therapeutic agents used in treatment are discussed below, and an integrated approach to care is discussed subsequently.

A comprehensive treatment approach involves avoiding and reducing asthma triggers and, if necessary, the adjunctive use of medications. Asthma medications are primarily divided into those that relax smooth muscle and produce a fairly rapid relief of acute symptoms and those that target inflammation or mediator production. The former medications are commonly referred to as reliever medications, and the latter are known as controller medications.

REDUCING TRIGGERS

Mitigation As shown in Tables 287-1 and 287-2, triggers and exposures can cause asthma and make it difficult to control. In

TABLE 287-4 Goals of Asthma Therapy

1. Reduction in symptom frequency to 2 times/week
2. Reduction of nighttime awakenings to 2 times/month
3. Reduction of reliever use to 2 times a week (except before exercise)
4. No more than 1 exacerbation/year
5. Optimization of lung function
6. Maintenance of normal daily activities
7. Satisfaction with asthma care with minimal or no side effects of treatment

the case of those with occupational exposures, removal from the offending environment may sometimes result in complete resolution of symptoms or significant improvement. Secondhand smoke exposure and frequent exposure to combustion products of cannabis are remediable environmental exposures as well. The removal of pets that are clearly associated with symptoms can reduce symptoms. Pest control at home and in the school in those with evidence of IgE-mediated sensitivity (skin test or IgE RAST) may also be beneficial. The effect of dust or mold control in reducing asthma symptoms has been more variable. There is moderate evidence that dust control (impermeable mattress and pillowcase covers) in those patients with symptoms and sensitization may be effective in reducing symptoms *only* when conducted as part of a comprehensive allergen mitigation strategy.

Allergen Immunotherapy Allergen immunotherapy reduces IgE-mediated reactions to the allergens administered. It clearly reduces the symptoms of allergic rhinitis and thus may be helpful in reducing this comorbidity. The evidence for its effectiveness in isolated asthma in those who are sensitized and have clinical symptoms is variable. Due to the risk of anaphylaxis, guidelines generally recommend immunotherapy only in patients whose asthma is under control and who have mild to moderate asthma. The evidence base for the effectiveness of sublingual allergen immunotherapy in the treatment of asthma is not substantial.

Vaccination Respiratory infections are a major cause of asthma exacerbations. Patients with asthma are strongly advised to receive both types of currently available pneumococcal vaccines and yearly influenza vaccines. COVID-19 vaccination is advised, as well.

MEDICATIONS

Bronchodilators Bronchodilators relax airway smooth muscle. There are three major classes of bronchodilators, β_2 -agonists, anticholinergics, and theophylline.

β_2 -Agonists Available in inhaled or oral form, these agents activate β_2 -receptors present on airway smooth muscle. Such receptors are also present on mast cells, but they contribute little to the efficacy of these agents in asthma. β_2 -receptors are G protein-coupled receptors that activate adenyl cyclase to produce cyclic AMP, which results in relaxation of smooth muscle.

Use β_2 -Agonists are primarily used in inhaled forms to provide relief of bronchospasm or to reduce the degree of bronchospasm anticipated in response to exercise or other provocative stimuli. Regular use has been associated with tachyphylaxis of the bronchoprotective effect and possible increased airway reactivity. This may be more common in patients with a polymorphism at the 16th amino acid position of the β_2 -receptor. Frequent short-acting β_2 -agonist use has been associated with increased asthma mortality resulting in decreased enthusiasm for use in isolation without inhaled corticosteroids.

Short-Acting β_2 -Agonists Albuterol (also known as salbutamol) is the most commonly used agent. Bronchodilation begins within 3–5 min of inhalation, and effects generally last 4–6 h. It is most commonly administered by metered-dose inhaler. Solutions for nebulization are also used, especially for relief of bronchospasm in children. Oral forms are available but are not commonly used.

Long-Acting β_2 -Agonists Salmeterol and formoterol are the two available LABAs. They have an ~12-h duration of action. Formoterol has a quick onset comparable to the short-acting β_2 -agonists. Salmeterol has a slower onset of action. These agents can be used for prophylaxis of exercise-induced bronchospasm. In contrast to their use in chronic obstructive pulmonary disease (COPD), these agents are *not* recommended for use as monotherapy in the treatment of asthma. Their use in asthma is generally restricted to use in combination with an ICS.

Ultra-Long-Acting β_2 -Agonists These agents (indacaterol, olodaterol, and vilanterol) have a 24-h effect. They are only used in combination with ICSs in the treatment of asthma.

Safety β_2 -Agonists are fairly specific for the β_2 -receptors, but in some patients and especially at higher doses, they can produce tremor, tachycardia, palpitations, and hypertension. They promote potassium reentry into cells, and at high doses, they can produce hypokalemia. Type B (nonhypoxic) lactic acidosis can also occur and is thought to be secondary to increased glycogenolysis and glycolysis and increased lipolysis, leading to a rise in fatty acid levels, which can inhibit conversion of pyruvate to acetyl-coenzyme A.

Increased asthma mortality was associated with high-potency β_2 -agonists in Australia and New Zealand. Increased use of β_2 -agonists for relief of bronchospasm is a clear marker of poor asthma control and has been associated with increased mortality. Questions had been raised as to whether adding LABAs to ICSs might be associated with severe adverse asthma outcomes, but several studies have not detected such outcomes in comparison to maintaining the ICS dose.

Anticholinergics Cholinergic nerve-induced smooth-muscle constriction plays a role in asthmatic bronchospasm. Anticholinergic medications can produce smooth-muscle relaxation by antagonizing this mechanism of airway narrowing. Agents that have been developed for asthma have been pharmacologically designed to be less systemically absorbed so as to minimize their systemic anticholinergic effects. The long-acting agents in this class are known as long-acting muscarinic antagonists (LAMAs).

Use The short-acting agents in this class can be used alone for acute bronchodilation. They appear to be somewhat less effective than β_2 -agonists and have a slower onset of action as well.

Safety Dry mouth may occur. At higher doses and in the elderly, acute glaucoma and urinary retention have been reported. There was a numerical (but not significant) difference in mortality in African Americans treated with ICS/LAMA versus ICS/LABA for asthma.

Theophylline Theophylline, an oral compound that increases cyclic AMP levels by inhibiting phosphodiesterase, is now rarely used for asthma due to its narrow therapeutic window, drug-drug interactions, and reduced bronchodilation as compared to other agents.

Controller (Anti-Inflammatory/Antimediator) Therapies So-called “controller” therapies reduce asthma exacerbations and improve long-term control, decreasing the need for intermittent use of bronchodilator therapies. None of these therapies have yet been shown to prevent progression of airway remodeling or the more rapid decline in lung function that can occur in a subset of asthma patients.

Corticosteroids Corticosteroids are particularly effective in reducing type 2 inflammation and airway hyperresponsiveness. Corticosteroids bind to a cytoplasmic glucocorticoid receptor to form a complex that translocates to the nucleus. The complex binds to positive and negative response elements that result in inhibition of T-cell activation; eosinophil function, migration, and proliferation; and proinflammatory cytokine elaboration and activation of

nuclear factor- B. It also attaches to other transcription factors, resulting in deactivation of other proinflammatory pathways.

Use Corticosteroids reduce airway hyperresponsiveness, improve airway function, prevent asthma exacerbations, and improve asthma symptoms. Corticosteroid use by inhalation (ICSs) minimizes systemic toxicity and represents a cornerstone of asthma treatment.

ICS and ICS/LABA ICSs are the cornerstone of asthma therapy. They take advantage of the pleiotropic effects of corticosteroids to produce salutary impact at levels of systemic effect considerably lower than oral corticosteroids. Their use is associated with decreased asthma mortality. They are generally used regularly twice a day as first-line therapy for all forms of persistent asthma. Doses are increased, and they are combined with LABAs to control asthma of increasing severity. European guidelines now recommend their intermittent use even in intermittent asthma. Combining them with LABAs permits effective control at lower ICS dose. Longer-acting preparations permitting once-a-day use are available. Their effects can be noticeable in several days, but continued improvement may occur over months of therapy, with the majority of improvement evident within the first month of regular use. Adherence to regular therapy is generally poor, with as few as 25% of total annual prescriptions being refilled. Very high doses are sometimes used to reduce oral corticosteroid requirements. Not all patients respond to ICS. Increasing evidence suggests that the most responsive patients are those with significant type 2-mediated asthma.

Oral Corticosteroids Chronic oral corticosteroids (OCSs) at the lowest doses possible (due to side effects) are used in patients who cannot achieve acceptable asthma control without them. Alternate-day dosing may be preferred, and pneumocystis pneumonia prophylaxis should be administered for those maintained on a daily prednisone dose of 20 mg. OCSs are also used to treat asthma exacerbations, frequently at a dose of 40–60 mg/d of prednisone or equivalent for 1–2 weeks. Since they are well absorbed, they may also be used for managing hospitalized patients.

Intravenous Corticosteroids Intravenous preparations are frequently used in hospitalized patients. Patients are rapidly transitioned to OCS once their condition has stabilized.

Intramuscular Corticosteroids In high-risk, poorly adherent patients, intramuscular triamcinolone acetonide has been used to achieve asthma control and reduce exacerbations.

Safety Chronic administration of systemic corticosteroids is associated with a plethora of side effects including diabetes, osteoporosis, cataracts and glaucoma, bruising, weight gain, truncal obesity, hypertension, ulcers, depression, and accelerated cardiac risk, among others. Appropriate monitoring and infectious (pneumocystis pneumonia prophylaxis for those treated chronically with 20 mg prednisone/d) and bone health prophylaxis are necessary. Intermittent “bursts” of systemic corticosteroids to treat asthma exacerbations are associated with reduced side effects, but observational studies have suggested that the cumulative dose over time is associated with deleterious side effects.

ICSs have dramatically reduced side effects as compared to OCSs. At higher doses, bruising occurs and osteoporosis can accelerate. There is a small increase in glaucoma and cataracts. Local effects include thrush, which can be reduced by use of a spacer and gargling. Hoarseness may be the result of a direct myopathic effect on the vocal cords. Rare patients exhibit side effects even at moderate doses of ICS. Children may experience growth suppression.

Leukotriene Modifiers Agents that inhibit production of leukotrienes (zileuton, an inhibitor of 5-lipoxygenase) or the action of leukotrienes at the CysLT₁ receptor (montelukast and zafirlukast) are moderately effective in asthma.

They can improve airway function and reduce exacerbations but not to the same degree as bronchodilators or ICS, respectively. They are also effective in reducing symptoms of allergic rhinitis and, thus,

can be used in patients with concomitant allergic rhinitis. Montelukast, in particular, is frequently used in children with mild asthma due to concerns of ICS-related growth suppression. Montelukast use may decrease due to safety warnings regarding depression with this compound. Leukotriene modifiers are effective in preventing exercise-induced bronchoconstriction without the tachyphylactic effects that occur with regular use of LABAs. Leukotriene modifiers are particularly effective in aspirin-exacerbated respiratory disease, which is characterized by significant leukotriene overproduction. They have also shown modest effect as add-on therapy in patients poorly controlled on high-dose ICS/LABA.

CysLT Antagonists Montelukast and zafirlukast are administered orally once or twice daily, respectively. The onset of effect is rapid (hours), with the majority of chronic effectiveness seen within 1 month.

5-Lipoxygenase Inhibition Zileuton in its extended form is administered orally twice a day.

Safety Montelukast is well tolerated, but an association with suicidal ideation has now resulted in a warning label from the U.S. Food and Drug Administration. Zileuton increases liver function tests (transaminases) in 3% of patients. Intermittent monitoring is suggested. It inhibits CYP1A2, and appropriate dose adjustments of concomitant medications may be necessary.

Cromolyn Sodium Cromolyn sodium is an inhaled agent believed to stabilize mast cells. It is only available by nebulization and must be administered two to four times a day. It is mildly to modestly effective and appears to be helpful for exercise-induced bronchospasm. It is used primarily in pediatrics in those concerned about ICS side effects.

Anti-IgE Omalizumab, a monoclonal antibody to the Fc portion of the IgE molecule, prevents the binding of IgE to mast cells and basophils. Reduction in free IgE that can bind to effector cells blocks antigen-related signaling, which is responsible for production or release of many of the mediators and cytokines critical to asthma pathobiology. In addition, through feedback mechanisms, reduction in IgE production occurs as well. Anti-IgE has been shown to increase interferon production in rhinovirus infections, decrease viral-induced asthma exacerbations, and reduce duration and peak viral shedding. This effect is believed to be due to IgE's ability to reduce interferon production in response to viral infections.

Use In asthma, anti-IgE has been tested in patients with a circulating IgE 30 IU/mL and a positive skin test or RAST to a perennial allergen. It is generally used in patients not responsive to moderate- to high-dose ICS/LABA. It reduces exacerbations by 25–50% and can reduce asthma symptoms but has minimal effect on lung function. Anti-IgE is dosed based on body weight and circulating IgE and is administered subcutaneously every 2–4 weeks depending on the calculated dose. In the United States, the maximum dose is 300 mg every 2 weeks, which generally restricts the drug to those with a body weight 150 kg . Most effects are generally seen in 3–6 months. Retrospective studies have suggested that patients with an exhaled nitric oxide approximately 20 ppb or circulating eosinophils $260/\mu\text{L}$ have the greatest response as ascertained by reduction in exacerbations. FeNO is slightly reduced by treatment, but circulating IgE, as measured by available clinical tests, is not affected since these tests measure total circulating IgE, not free IgE.

Safety The incidence of side effects is low. Anaphylaxis has been reported in 0.2% of patients receiving the drug.

IL-5-Active Drugs Mepolizumab and reslizumab are monoclonal antibodies that bind to IL-5, and benralizumab binds to the IL-5 receptor. They rapidly (within a day) reduce circulating eosinophils.

Use In patients symptomatic on moderate- to high-dose ICS/LABA, generally with two or more exacerbations that require OCS per year and with an eosinophil count of $300/\mu\text{L}$, IL-5-active drugs reduce exacerbations by about half or more. FEV₁ and symptoms

improve moderately as well. In patients who are not on chronic OCSs, these drugs are less effective in those with eosinophil counts $<300/\mu\text{L}$. They are also effective in reducing the need for chronic OCSs regardless of circulating eosinophil count (presumably due to the fact that many of those patients have type 2 inflammation but their circulating eosinophils have been suppressed by the systemic OCS). FeNO and IgE are relatively unaffected by these drugs. Most clinical effects are usually seen within 3–6 months.

Safety These drugs are associated with minimal side effects. Mepolizumab and benralizumab are approved for home administration.

Anti-IL-4/13 The IL-4 and IL-13 receptors are heterodimers that share a common subunit, IL-4 receptor α . Dupilumab binds to this subunit and, thus, blocks signaling through both receptors.

Use In addition to effectiveness in the phenotype of patients who respond to anti-IL-5 therapies, poorly controlled patients on moderate- to high-dose ICS/LABA with an FeNO of 20–25 ppb also appear to respond to dupilumab even if their peripheral eosinophils are not elevated. Dupilumab reduces exacerbations by 50%, decreases symptoms, and may produce more of an effect on FEV₁ than anti-IL-5 drugs. It gradually reduces FeNO and IgE levels. Paradoxically, circulating eosinophil counts may initially temporarily increase. Most effects are seen by 3–6 months of therapy.

Safety Side effects are minimal but cases of serious systemic eosinophilia associated with the reduction of oral corticosteroids have been noted. This drug is also approved for home administration and is also approved for atopic dermatitis.

Bronchial Thermoplasty, Alternative Therapies, and Therapies Under Development • **Bronchial Thermoplasty** This procedure involves radiofrequency ablation of the airway smooth muscle in the major airways administered through a series of three bronchoscopies for patients with severe asthma. There is some evidence that it may reduce exacerbations in very select patients. The procedure may be accompanied by significant morbidity, and most guidelines do not recommend it other than in the context of clinical trials or registries.

Alternative Therapies Alternative therapies such as acupuncture and yoga have not been shown to improve asthma in controlled trials. Studies with placebo have demonstrated that there may be a significant response to placebo.

Therapies in Development Trials are underway targeting pathways and receptors shown in Fig. 287-3. Those in more advanced stages of development include therapies targeting TSLP, IL-33, and CTRH₂. Studies targeting IL-17 and TNF- α have not shown efficacy, but it is unclear if they were appropriately targeted. Whether these interventions might prove useful for particular endotypes of asthma is unclear. Proof-of-concept studies targeting mast cells via inhibition of tyrosine kinase have suggested efficacy in severe asthma.

APPROACH TO THE PATIENT

Asthma

U.S. (National Asthma Education and Prevention Program [NAEPP]) and World Health Organization (Global Initiative for Asthma [GINA]) guidelines advise a symptomatic approach to asthma treatment assuming that appropriate measures have been taken to address asthma triggers, exposures, and comorbidities enumerated in Tables 287-2 and 287-3. Additionally, adherence and inhaler techniques need to be addressed. Poor adherence or poor inhaler technique has been identified as the cause of poor asthma control in up to 50% of patients referred for poorly controlled asthma.

The stepwise approach to intensifying and reducing asthma therapy is outlined in Table 287-5. It involves “stepping” therapy up or down based on assessment of whether asthma is controlled by

TABLE 287-5 Step Therapy for the Treatment of Asthma Ages 12+ (modified from GINA and NAEPP)

	Address exposures and comorbidities (see Tables 287-2 and 287-3) Confirm inhaler technique and optimize adherence Move up or down steps based on control (see Table 287-3)					
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred regular therapy	None	None ^a or low-dose ICS ^b	Low-dose ICS/ formoterol	Medium-dose ICS/formoterol	Medium to high-dose ICS/LABA, + add-on LAMA	Anti-IgE or anti-IL-5 or anti-IL4-R α ; step 5 therapy as required
Alternative regular therapy	None	LTRA	Medium-dose ICS	High-dose ICS	Anti-IgE or anti-IL-5 or anti-IL4-R α	OCS ^c
Adjunctive therapy				LTM and/or LAMA (especially LAMA at Step 5)		
As-needed reliever therapy	ICS/formoterol (low dose) or SABA ^b	ICS/formoterol (low dose), or PRN concomitant ICS and SABA ^b or SABA ^e			ICS/formoterol (low dose) ^d	

^aIf using as-needed ICS/formoterol or PRN concomitant ICS & SABA, this is an option. ^bNational Asthma Education and Prevention Program (NAEPP) recommendation. ^cTo be avoided as much as possible. ^dPRN ICS/formoterol only suggested for steps 3 and 4 by NAEPP. ^eIf using low-dose ICS as regular therapy.

Abbreviations: ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β -agonist; LAMA, long-acting muscarinic antagonist; LTM, leukotriene modifier; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRN, as needed; SABA, short-acting β -agonist.

the criteria listed in Table 287-4. Assuming comorbidities have been addressed, adherence has been evaluated, education regarding avoiding triggers has been performed, and inhaler technique is verified, the cornerstone of preferred therapy is the intensification of ICS therapy in conjunction with the use of a LABA to achieve greater control at lower ICS doses.

A major change in the stepwise approach, advocated for more than two decades, has occurred. Evidence has accumulated that as-needed ICS can be used instead of regular ICS in milder asthma and that the trigger for such use could be patient perception of the need to use a reliever inhaler. Since formoterol is a LABA with a rapid onset, combination ICS/formoterol has been used as a single agent in multiple studies: as needed without background therapy in milder asthma, and as needed in addition to twice daily ICS/formoterol in more severe asthma. Since asthma mortality can occur even in mild asthma (albeit at lower rates than more severe asthma), GINA, as part of a comprehensive strategy of asthma management, recommends ICS/formoterol be used as the reliever in all steps of asthma severity, including intermittent asthma (Step 1). NAEPP guidelines utilizing evidence-based studies recommend that ICS/formoterol be used as the reliever medication in patients requiring step 3 and 4 therapy (see Table 287-5) and that as-needed concomitant ICS and short-acting β -agonist (SABA) can be used as a therapy in step 2. For the sake of simplicity, an adapted GINA approach is outlined in Table 287-5 with footnotes identifying the major differences from the NAEPP. Leukotriene receptor antagonists (LTRAs) are alternative medications in step 2, which may be used in those concerned about the minimal ICS side effects. However, recent warnings about suicidal ideation associated with montelukast may make this approach less appealing. Leukotriene modifiers and long-acting anticholinergics are possible add-on (adjunctive) therapies in those requiring step 4 and/or 5 therapies. Biologics are incredibly effective in their specific endotypes (type 2 with exacerbations and specific biomarkers, as previously described), but their high cost currently relegates them to step 5 therapy or beyond.

TREATMENT

Asthma Attacks

Asthma deteriorations of mild to moderate severity can be initially treated with a β -agonist administered up to every 1 h. Increasing the dose of ICSs by four- to fivefold may be helpful as well. If patients fail to achieve adequate control and continue to require β -agonists hourly for several hours, they should be referred for

urgent care. In the urgent care setting, PEFR or FEV₁ should be assessed, and patients are usually treated with nebulized β -agonists up to every 20 min. Those with PEFR >60% of predicted will frequently respond to β -agonists alone. If they fail to respond in 1–2 h, intravenous corticosteroids should be administered. Supplemental oxygen is usually administered to correct hypoxemia. An LTRA and magnesium are sometimes given as well. Nebulized anticholinergics can be administered to produce additional bronchodilation. Failure to achieve PEFR >60% or persistent severe tachypnea over 4–6 h should prompt consideration of admission to the hospital. In-hospital treatment may include continuous bronchodilator nebulization. Noninvasive positive-pressure ventilation to assist with respiratory exhaustion is sometimes used to prevent a need for intubation, and helium-oxygen mixtures may be used to decrease the work of breathing. Antibiotics should be administered only if there are signs of infection.

Mechanical ventilation may be difficult in patients with status asthmaticus due to high positive pressures in the setting of high resistance to airflow due to airway obstruction. Most patients with asthma attacks present with hypoxemia due to a high respiratory rate. Normal or near-normal PCO₂ in a patient with asthma in respiratory distress should raise concerns of impending respiratory failure and need for mechanical ventilation. Mechanical ventilation should aim for low respiratory rates and/or ventilation volumes to decrease peak airway pressures. This can frequently be achieved by “permissive hypercapnia”—allowing the PCO₂ to rise and, if necessary, temporarily correcting critical acidosis with administration of fluids to increase the pH. Neuromuscular paralysis may sometimes be beneficial. Bronchoscopy to clear mucus plugs has been described but may be dangerous in the setting of difficulties with mechanical ventilation.

SPECIAL CONSIDERATIONS

HIGH-RISK ASTHMA PATIENTS

Three to four thousand people die from asthma in the United States each year. Table 287-6 lists characteristics of patients at high risk for asthma death. These characteristics should be considered in evaluating and treating patients who present with asthma.

EXERCISE-INDUCED SYMPTOMS

In many cases, the degree of exercise intolerance may reflect poor asthma control. Treatment involves step therapy of asthma as outlined in Table 287-5. In other cases, however, asthma may be well controlled in all other respects, but patients may report that they cannot undertake the level of exercise they desire. Some increase in exercise capacity

TABLE 287-6 Patients at Greater Risk for Asthma Mortality

1. History of intensive care unit admission for asthma
2. History of intubation for asthma
3. Illicit drug use
4. Depression
5. New diagnosis
6. 2 emergency unit visits in past 6 months
7. Severe psychosocial problems
8. Lower socioeconomic status
9. On daily prednisone prior to admission

can be achieved by starting at lower levels of exercise (warming up) and by using a mask in colder weather to condition the air. Pretreatment with an SABA can increase the threshold of ventilation required to induce bronchoconstriction. LABAs may extend the period of protection, but their use alone in asthma is to be discouraged. For occasional exercise, ICS/LABA can be used, but regular use may expose the patient to unnecessary doses of ICS. If regular exercise is undertaken, then LTRAs may provide protection and can be used regularly. A SABA (or ICS/formoterol) should always be available for quick relief.

Exercise-induced airway narrowing in elite athletes may be related to direct epithelial injury. In addition to the above, conditioning of incoming air may be of major assistance. Ipratropium has been reported to be of utility as well.

PREGNANCY

Asthma may improve, deteriorate, or remain unchanged during pregnancy. Poor asthma control, especially exacerbations, is associated with poor fetal outcomes. The general principles of asthma management and its goals are unchanged. Avoidance of triggers, especially smoking environments, is critical in view of the risk of loss of control and, in the case of smoking, its clear effects on risk of development of asthma in the child. There is extensive experience suggesting the safety of inhaled albuterol, beclomethasone, budesonide, and fluticasone, with reassuring information on formoterol and salmeterol in pregnancy. Animal studies have not suggested toxicity for montelukast, zafirlukast, omalizumab, and ipratropium. Antibodies cross the placenta, and there are few human data on the safety of IL-5-active drugs or anti-IL-4R. Chronic use of OCS has been associated with neonatal adrenal insufficiency, preeclampsia, low birth weight, and a slight increase in the frequency of cleft palate. However, it is clear that poorly controlled asthma during pregnancy carries greater risk to the fetus and mother than these effects. There should be no hesitancy in administering routine pharmacotherapy for acute exacerbations. Initiation of allergen immunotherapy or omalizumab during pregnancy is not recommended. In cases where prostaglandins are needed to manage pregnancy, PGF2-should be avoided since it is associated with bronchoconstriction.

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

A subset of patients (5–10%) present in adulthood with difficult-to-control asthma and type 2 inflammation with eosinophilia, sinusitis, nasal polypsis, and severe asthma exacerbations that are precipitated by ingesting inhibitors of cyclooxygenase, with aspirin being the most prominent of such inhibitors. Such patients, classified as having aspirin-exacerbated respiratory disease, overproduce leukotrienes in response to inhibition of cyclooxygenase-1, probably secondary to inhibition of PGE₂. These patients should avoid inhibitors of cyclooxygenase-1, (aspirin and NSAIDs) but can generally tolerate inhibitors of cyclooxygenase-2 and acetaminophen. They should be treated with leukotriene modifiers. Aspirin desensitization can be undertaken to decrease upper respiratory symptoms and to allow chronic administration of aspirin or NSAIDs for those that require it. Dupilumab and the IL-5-active biologics appear to be particularly helpful and appear to be superseding aspirin desensitization in management except when chronic administration of aspirin or NSAIDs is required for another therapeutic indication.

SEVERE ASTHMA

Severe and difficult-to-treat asthma, which composes ~5–10% of asthma, is defined as asthma that, having undergone appropriate evaluation for comorbidities and mimics, education, and trigger mitigation, remains uncontrolled on step 5 therapy or requires step 5 therapy for its control. Severe asthma can account for almost 50% of the cost of asthma care in the United States. A significant proportion of these patients have trouble with adherence and/or inhaler technique, and these factors need to be investigated vigorously. Almost half of these patients have evidence of persistent eosinophilic inflammation as evidenced by peripheral blood eosinophils and/or induced sputum. Those with recurrent exacerbations have a substantially increased likelihood of responding to the type 2 targeted biologics. Treatment for those with mixed inflammation, isolated neutrophilic inflammation, or pauci-granulocytic inflammation remains to be determined. Some data suggest that many of these patients may have aberrations in the pathways responsible for resolution of inflammation. A rare patient may have biochemical abnormalities that interfere with steroid response pathways. Macrolides are of use in a subset. Studies targeting mast cells, IL-6, IL-33, and other pathways illustrated in Fig. 287-3 are underway. Therapies aimed at improving pro-resolving pathways may also be promising.

ELDERLY PATIENTS WITH ASTHMA

Asthma may present at or persist into older age. The mortality of asthma in those >65 years old is five times greater than that of younger cohorts even when adjusting for comorbidities. Many of these patients had asthma as children, some with quiescent periods as they entered adulthood. Of those with new-onset asthma, almost half were smokers or are currently smoking. One-quarter of adult-onset asthma is believed to be due to occupational exposure. Patients presenting with eosinophilic inflammation appear to have more severe asthma. Besides investigations of comorbidities, these patients may require adjustment to step therapy based on intolerance of β_2 -agonist therapy due to arrhythmia or tremulousness. The coexistence of COPD needs to be carefully considered (see below).

ASTHMA-COPD OVERLAP

Most clinicians agree that asthma-COPD overlap is not a syndrome, but rather recognize that it may be useful to identify patients who present with symptoms related to airway dysfunction that may be due to simultaneous coexistence of both asthma and COPD. From an asthma perspective, recognition that COPD and smoking can alter the response to asthma therapies may be important. Smoking can blunt the response to ICS. Further, it has been difficult to demonstrate the effectiveness of biologic agents targeted at type 2 inflammation in patients with COPD despite the presence of 300 circulating eosinophils/ μ L. Additionally, in patients with both diseases, earlier initiation of anticholinergics may be considered.

Acknowledgment

Peter J. Barnes contributed to this chapter in the 20th edition, and some material from that chapter has been retained here.

FURTHER READING

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HYPERSENSITIVITY PNEUMONITIS

INTRODUCTION AND DEFINITION

Hypersensitivity pneumonitis (HP), also referred to as extrinsic allergic alveolitis, is a pulmonary disease that occurs due to inhalational exposure to a variety of antigens leading to an inflammatory response of the alveoli and small airways. Systemic manifestations such as fever and fatigue can accompany respiratory symptoms. Although sensitization to an inhaled antigen as manifested by specific circulating IgG antibodies is necessary for the development of HP, sensitization alone is not sufficient as a defining characteristic, because many sensitized individuals do not develop HP. The incidence and prevalence of HP are variable, depending on geography, occupation, avocation, and environment of the cohort being studied. As yet unexplained is the decreased risk of developing HP in smokers.

OFFENDING ANTIGENS

HP can be caused by any of a large list of potential offending inhaled antigens (**Table 288-1**). The various antigens and environmental conditions described to be associated with HP give rise to an expansive list of monikers given to specific forms of HP. Antigens derived from fungal, bacterial, mycobacterial, bird-derived, and chemical sources have all been implicated in causing HP.

Categories of individuals at particular risk in the United States include farmers, bird owners, industrial workers, and hot tub users. Farmer's lung occurs as a result of exposure to one of several possible sources of bacterial or fungal antigens such as grain, moldy hay, or silage. Potential offending antigens include thermophilic actinomycetes or *Aspergillus* species. Bird fancier's lung (also referred to by names corresponding to specific birds) must be considered in patients who give a history of keeping birds in their home and is precipitated by exposure to antigens derived from feathers, droppings, and serum proteins. Occupational exposure to birds may also cause HP, as is seen in poultry worker's lung. Chemical worker's lung is provoked by exposure to occupational chemical antigens such as diphenylmethane diisocyanate and toluene diisocyanate. Mycobacteria may cause HP rather than frank infection, a phenomenon observed in hot tub lung and in HP due to metalworking fluid.

PATOPHYSIOLOGY

While much remains to be learned regarding the pathophysiology of HP, it has been established that HP is an immune-mediated condition that occurs in response to inhaled antigens that are small enough to deposit in distal airways and alveoli. From an immunologic perspective, HP is characterized by dysregulated T_H1 and T_H17 immune responses. Although the presence of precipitating IgG antibodies against specific antigens in HP suggests a prominent role for adaptive immunity in the pathophysiology of HP, innate immune mechanisms likely also make an important contribution. This is highlighted by the observation that Toll-like receptors and downstream signaling proteins such as MyD88 are activated in HP, leading to neutrophil recruitment. Although no clear genetic basis for HP has been established, in specific cohorts, polymorphisms in genes involved in antigen processing and presentation, including TAP1 and major histocompatibility complex type II, have been observed. In chronic HP, bone marrow-derived fibrocytes may contribute to lung inflammation and fibrosis.

TABLE 288-1 Examples of Hypersensitivity Pneumonitis

DISEASE	ANTIGEN	SOURCE
Farming/Food Processing		
Farmer's lung	Thermophilic actinomycetes (e.g., <i>Saccharopolyspora rectivirgula</i>); fungus	Grain, moldy hay, silage
Bagassosis	Thermophilic actinomycetes	Sugarcane
Cheese washer's lung	<i>Penicillium casei</i> ; <i>Aspergillus clavatus</i>	Cheese
Coffee worker's lung	Coffee bean dust	Coffee beans
Malt worker's lung	<i>Aspergillus</i> species	Barley
Miller's lung	<i>Sitophilus granarius</i> (wheat weevil)	Wheat flour
Mushroom worker's lung	Thermophilic actinomycetes; mushroom spores	Mushrooms
Potato riddler's lung	Thermophilic actinomycetes; <i>Aspergillus</i> species	Moldy hay around potatoes
Tobacco grower's lung	<i>Aspergillus</i> species	Tobacco
Wine maker's lung	<i>Botrytis cinerea</i>	Grapes
Birds and Other Animals		
Bird fancier's lung (also named by specific bird exposures)	Proteins derived by parakeets, pigeons, budgerigars	Bird feathers, droppings, serum proteins
Duck fever	Duck feathers, serum proteins	Ducks
Fish meal worker's lung	Fish meal dust	Fish meal
Furrier's lung	Dust from animal furs	Animal furs
Laboratory worker's lung	Rat urine, serum, fur	Laboratory rats
Pituitary snuff taker's lung	Animal proteins	Pituitary snuff from bovine and porcine sources
Poultry worker's lung	Chicken serum proteins	Chickens
Turkey handling disease	Turkey serum proteins	Turkeys
Other Occupational and Environmental Exposures		
Chemical worker's lung	Isocyanates	Polyurethane foam, varnish, lacquer
Detergent worker's lung	<i>Bacillus subtilis</i> enzymes	Detergent
Hot tub lung	<i>Cladosporium</i> species; <i>Mycobacterium avium</i> complex	Contaminated water, mold on ceiling
Humidifier fever (and air conditioner lung)	Several microorganisms including: <i>Aureobasidium pullulans</i> ; <i>Candida albicans</i> ; thermophilic actinomycetes; <i>Mycobacterium</i> species; <i>Klebsiella oxytoca</i> ; <i>Naegleria gruberi</i>	Humidifiers and air conditioners (contaminated water)
Machine operator's lung	<i>Pseudomonas</i> species; <i>Mycobacteria</i> species	Metal working fluid
Sauna taker's lung	<i>Aureobasidium</i> species; other antigens	Sauna water
Suberosis	<i>Penicillium glabrum</i> ; <i>Chrysosporium sitophila</i>	Cork dust
Summer-type pneumonitis	<i>Trichosporon cutaneum</i>	House dust mites, bird droppings
Woodworker's lung	<i>Alternaria</i> species; <i>Bacillus subtilis</i>	Oak, cedar, pine, mahogany dusts

CLINICAL PRESENTATION

Given the heterogeneity among patients, variability in offending antigens, and differences in the intensity and duration of exposure to antigen, the presentation of HP is accordingly variable. Although these categories are not fully satisfactory in capturing this variability, HP has been traditionally categorized as having *acute*, *subacute*, and *chronic* forms. Acute HP usually manifests itself 4–8 h following exposure to the inciting antigen, often intense in nature. Systemic symptoms,

including fevers, chills, and malaise, are prominent and are accompanied by dyspnea. Symptoms resolve within hours to days if no further exposure to the offending antigen occurs. In subacute HP resulting from ongoing antigen exposure, the onset of respiratory and systemic symptoms is typically more gradual over the course of weeks. A similar presentation may occur as a culmination of intermittent episodes of acute HP. Although respiratory impairment may be quite severe, antigen avoidance generally results in resolution of the symptoms, but with a slower time course, on the order of weeks to months, than that seen with acute HP. Chronic HP can present with an even more gradual onset of symptoms than subacute HP, with progressive dyspnea, cough, fatigue, weight loss, and clubbing of the digits. The insidious onset of symptoms and frequent lack of an antecedent episode of acute HP make diagnosing chronic HP a challenge. Unlike with the other forms of HP, there can be an irreversible component to the respiratory impairment that is not responsive to removal of the responsible antigen from the patient's environment. The disease progression of chronic HP to lung fibrosis with honeycombing on chest imaging and hypoxic respiratory failure can mirror that seen in idiopathic pulmonary fibrosis (IPF), with a similar prognosis. Diagnostic uncertainty between these two entities is not uncommon. Fibrotic lung disease is a potential feature of chronic HP due to exposure to bird antigens, whereas an emphysematous phenotype may be seen in farmer's lung.

The categories of acute, subacute, and chronic HP are not completely sufficient in classifying HP. The HP Study Group found on cluster analysis that a cohort of HP patients is best described in bipartite fashion, with one group featuring recurrent systemic signs and symptoms and the other featuring more severe respiratory findings. Some experts have argued for a reclassification of HP into acute/inflammatory and chronic/fibrotic categories.

Concordant with the variability in the presentation of HP is the observed variability in outcome. HP that has not progressed to chronic lung disease has a more favorable outcome with likely resolution if antigen avoidance can be achieved. However, chronic HP resulting in lung fibrosis has a poorer prognosis, with patients with chronic pigeon breeder's lung having demonstrated a similar mortality as seen in IPF.

DIAGNOSIS

Although there is no set of universally accepted criteria for arriving at a diagnosis of HP, diagnosis depends foremost on establishing a history of exposure to an offending antigen that correlates with respiratory and systemic symptoms. A careful occupational and home exposure history should be taken and may be supplemented if necessary by a clinician visit to the work or home environment. Specific inquiries will be influenced by geography and the occupation of the patient. When HP is suspected by history, the additional workup is aimed at establishing an immunologic and physiologic response to inhalational antigen exposure with chest imaging, pulmonary function testing (PFT), serologic studies, bronchoscopy, and, on occasion, lung biopsy. Re-exposure to the offending environment may be performed to aid in confirming the diagnosis of HP.

Chest Imaging Chest x-ray findings in HP are nonspecific and can even lack any discernible abnormalities. In cases of acute and subacute HP, findings may be transient and can include ill-defined micronodular opacities or hazy ground-glass airspace opacities. Findings on chest x-ray will often resolve with removal from the offending antigen, although the time course of resolution may vary. With chronic HP, the abnormalities seen on the chest radiograph are frequently more fibrotic in nature and may be difficult to distinguish from IPF.

High-resolution computed tomography (HRCT) is a common component in the diagnostic workup for HP. Although the HRCT may be normal in acute forms of HP, this may be due to lack of temporal correlation between exposure to the offending antigen and obtaining the imaging. Additionally, because of the transient nature of acute HP, HRCT is not always performed. In subacute forms of the disease, ground-glass airspace opacities are characteristic, as is the presence of centrilobular nodules. Expiratory images may show areas of air trapping that are likely caused by involvement of the small airways

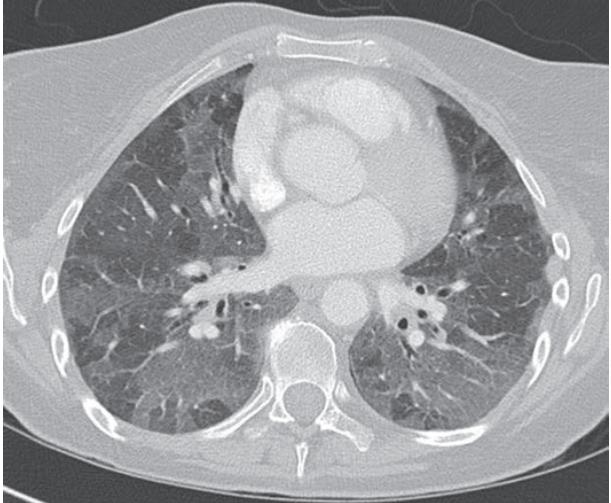


FIGURE 288-1 Chest computed tomography scan of a patient with subacute hypersensitivity pneumonitis in which scattered regions of ground-glass infiltrates in a mosaic pattern consistent with air trapping are seen bilaterally. This patient had bird fancier's lung. (Courtesy of TJ Gross; with permission.)

(Fig. 288-1). Reticular changes and traction bronchiectasis can be observed in chronic HP. Subpleural honeycombing similar to that seen in IPF may be present in advanced cases, although unlike in IPF, the lung bases are frequently spared.

Pulmonary Function Testing Either restrictive or obstructive PFTs can be present in HP, so the pattern of PFT change is not useful in establishing the diagnosis of HP. However, obtaining PFTs is of use in characterizing the physiologic impairment of an individual patient and in gauging the response to antigen avoidance and/or corticosteroid therapy. Diffusion capacity for carbon monoxide may be significantly impaired, particularly in cases of chronic HP with fibrotic pulmonary parenchymal changes.

Serum Precipitins Assaying for IgG antibodies against specific antigens, either through precipitin testing or direct serum measurement, can be a useful adjunct in the diagnosis of HP. However, the presence of an immunologic response alone is not sufficient for establishing the diagnosis, because many asymptomatic individuals with high levels of exposure to antigen may display specific IgG, as has been observed in farmers and in pigeon breeders. It should also be noted that panels that test for several specific antigens often provide false-negative results, because they represent an extremely limited proportion of the universe of potential offending environmental antigens.

Bronchoscopy Bronchoscopy with bronchoalveolar lavage (BAL) may be used in the evaluation of HP. Although not a specific finding, BAL lymphocytosis is characteristic of HP. However, in active smokers, a lower threshold should be used to establish BAL lymphocytosis, because smoking will result in lower lymphocyte percentages. Most cases of HP have a CD4+/CD8+ lymphocyte ratio of <1, but again, this is not a specific finding and has limited utility in the diagnosis of HP.

Lung Biopsy Tissue samples may be obtained by a bronchoscopic approach using transbronchial biopsy, or more architecturally preserved specimens may be obtained by a surgical approach (video-assisted thoracoscopy or open approach). As is the case with BAL, histologic specimens are not absolutely necessary to establish the diagnosis of HP, but they can be useful in the correct clinical context. A common histologic feature in HP is the presence of noncaseating granulomas in the vicinity of small airways (Fig. 288-2). As opposed to pulmonary sarcoidosis, in which noncaseating granulomas are well defined, the granulomas seen in HP are loose and poorly defined in nature. Within the alveolar spaces and in the interstitium, a mixed cellular infiltrate with a lymphocytic predominance is observed that is frequently patchy

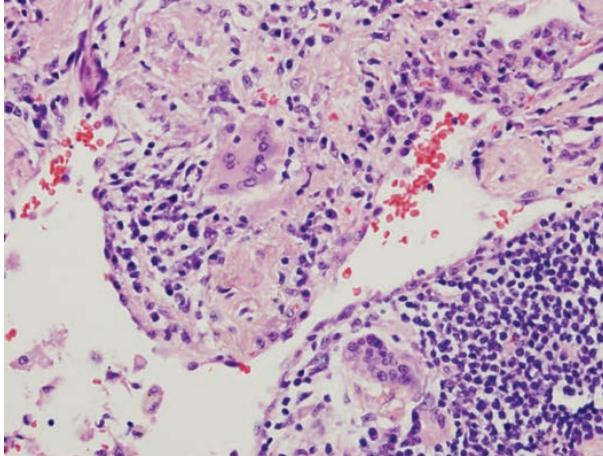


FIGURE 288-2 Open-lung biopsy from a patient with subacute hypersensitivity pneumonitis demonstrating a loose, nonnecrotizing granuloma made up of histiocytes and multinucleated giant cells. Peribronchial inflammatory infiltrate made up of lymphocytes and plasma cells is also seen. (*Courtesy of TJ Gross; with permission.*)

in distribution. Bronchiolitis with the presence of organizing exudate is also often observed. Fibrosis may be present as well, particularly in chronic HP. Fibrotic changes may be focal but can be diffuse and severe with honeycombing in advanced cases, similar to findings in IPF.

Clinical Prediction Rule Although not meant as a set of validated diagnostic criteria, a clinical prediction rule for predicting the presence of HP has been published by the HP Study Group. They identified six statistically significant predictors for HP, the strongest of which was exposure to an antigen known to cause HP. Other predictive criteria were the presence of serum precipitins, recurrent symptoms, symptoms occurring 4–8 h after antigen exposure, crackles on inspiration, and weight loss.

DIFFERENTIAL DIAGNOSIS

Differentiating HP from other conditions that cause a similar constellation of respiratory and systemic symptoms requires an increased index of suspicion based on obtaining a history of possible exposure to an offending antigen. Presentations of acute or subacute HP can be mistaken for respiratory infection. In cases of chronic disease, HP must be differentiated from interstitial lung disease, such as IPF or nonspecific interstitial pneumonitis (NSIP); this can be a difficult task even with lung biopsy. Given the presence of pulmonary infiltrates and noncasingating granulomas on biopsy, sarcoidosis is also a consideration in the differential diagnosis of HP. Unlike in HP, however, hilar adenopathy may be prominent on chest x-ray, organs other than the lung may be involved, and noncaseating granulomas in pathologic specimens tend to be well formed. Other inhalational syndromes, such as organic toxic dust syndrome (OTDS), can be misdiagnosed as HP. OTDS occurs with exposure to organic dusts, including those produced by grains or mold silage, but neither requires prior antigen sensitization nor is characterized by positive specific IgG antibodies.

TREATMENT

Hypersensitivity Pneumonitis

The mainstay of treatment for HP is antigen avoidance, if possible. A careful exposure history must be obtained to attempt to identify the potential offending antigen and to identify the location where a patient is exposed. Once a potential antigen and location are identified, efforts should be made to modify the environment to minimize patient exposure. This may be accomplished with measures such as removal of birds, removal of molds, and improved

ventilation. Personal protective equipment including respirators and ventilated helmets can be used but may not provide adequate protection for sensitized individuals. In some cases, fully avoiding specific environments may be necessary, although such a recommendation must be balanced against the effects to an individual's lifestyle or occupation. It is not uncommon for patients with HP due to exposure to household birds to be unwilling to remove them from the home.

Because acute HP is generally a self-limited disease after a discrete exposure to an offending antigen, pharmacologic therapy is generally not necessary. However, in so-called subacute and chronic forms of the disease, there is a role for glucocorticoid therapy. In patients with particularly severe symptoms as a result of subacute HP, antigen avoidance may be insufficient after establishing the diagnosis. Although glucocorticoids do not change the long-term outcome in these patients, they can accelerate the resolution of symptoms. While there is significant variability in the approach to glucocorticoid therapy by individual clinicians, prednisone therapy can be initiated at 0.5–1 mg/kg of ideal body weight per day (not to exceed 60 mg/d or alternative glucocorticoid equivalent) over a duration of 1–2 weeks, followed by a taper over the next 2–6 weeks. In chronic HP, a similar trial of corticosteroids may be used, although a variable component of fibrotic disease may be irreversible. In advanced cases of chronic HP with extensive lung fibrosis, lung transplantation may be necessary.

GLOBAL CONSIDERATIONS

As the ever-expanding list of antigens and exposures associated with the development of HP suggests, populations at risk for HP will vary globally based on specifics of local occupational, avocational, and environmental factors. Specific examples of geographically limited HP include summer-type pneumonitis seen in Japan and suberosis seen in cork workers in Portugal and Spain.

PULMONARY INFILTRATES WITH EOSINOPHILIA

Although eosinophils are normal constituents of the lungs, there are several pulmonary eosinophilic syndromes that are characterized by pulmonary infiltrates on imaging along with an increased number of eosinophils in lung tissue, in sputum, and/or in BAL fluid, with resultant increased respiratory symptoms and the potential for systemic manifestations. Because the eosinophil plays such an important role in each of these syndromes, it is often difficult to distinguish between them, but there are important clinical and pathologic differences as well as differences in prognosis and treatment paradigms.

CLASSIFYING PULMONARY INFILTRATES WITH EOSINOPHILIA AND GENERAL APPROACH

Because there are so many different diagnoses associated with pulmonary infiltrates with eosinophilia, the first step in classifying pulmonary eosinophilic syndromes is distinguishing between primary pulmonary eosinophilic lung disorders and those with eosinophilia that are secondary to a specific cause such as a drug reaction, an infection, a malignancy, or another pulmonary condition such as asthma. **Table 288-2** lists primary and secondary pulmonary eosinophilic disorders.

For each patient, a detailed history is of utmost importance and can help elucidate what the underlying disease is. Details regarding onset, timing, and precipitants of specific symptoms can help discern one diagnosis from another. History regarding pharmacologic, occupational, and environmental exposures is instructive, and family and travel history are crucial. In addition to details about the sinuses and lungs, it is important to inquire about systemic manifestations and assess for physical findings of cardiac, gastrointestinal (GI), neurologic, dermatologic, and genitourinary involvement, all of which may give clues to specific diagnoses. Once the details from history and physical are teased out, laboratory testing (including measurements of blood eosinophils, cultures, and markers of inflammation), spirometry, and radiographic imaging

TABLE 288-2 Pulmonary Infiltrates with Eosinophilia**Primary Pulmonary Eosinophilic Disorders**

- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Hypereosinophilic syndrome

Pulmonary Disorders of Known Cause Associated with Eosinophilia

- Asthma and eosinophilic bronchitis
- Allergic bronchopulmonary aspergillosis
- Bronchocentric granulomatosis
- Drug/toxin reaction
- Infection (Table 288-4)
 - Parasitic/helminthic disease
 - Nonparasitic infection

Lung Diseases Associated with Eosinophilia

- Cryptogenic organizing pneumonia
- Hypersensitivity pneumonitis
- Idiopathic pulmonary fibrosis
- Pulmonary Langerhans cell granulomatosis

Malignant Neoplasms Associated with Eosinophilia

- Leukemia
- Lymphoma
- Lung cancer
- Adenocarcinoma of various organs
- Squamous cell carcinoma of various organs

Systemic Disease Associated with Eosinophilia

- Postradiation pneumonitis
- Rheumatoid arthritis
- Sarcoidosis
- Sjogren's syndrome

can help distinguish between different diseases. Often, however, BAL, transbronchial, or open lung biopsies are required. In many cases, biopsies or noninvasive diagnostic studies of other organs (e.g., echocardiogram, electromyogram, or bone marrow biopsy) can be helpful.

PATOPHYSIOLOGY

Pathologically, the pulmonary eosinophilic syndromes are characterized by tissue infiltration by eosinophils (Fig. 288-2). In eosinophilic granulomatosis with polyangiitis (EGPA), extravascular granulomas and necrotizing vasculitis may occur in the lungs, as well as in the heart, skin, muscle, liver, spleen, and kidneys, and may be associated with fibrinoid necrosis and thrombosis.

The exact etiology of the various pulmonary eosinophilic syndromes is unknown; however, it is felt that these syndromes result from dysregulated eosinophilopoiesis or an autoimmune process because of the prominence of allergic features and the presence of immune complexes, heightened T-cell immunity, and altered humoral immunity as evidenced by elevated IgE, IgG4, and rheumatoid factor. Because of its integral involvement in eosinophilopoiesis, interleukin 5 (IL-5) has been hypothesized to play an etiologic role. Monoclonal antibodies against IL-5 are now in clinical use for the treatment of eosinophilic asthma and eosinophilic granulomatosis with polyangiitis and are under investigation for other conditions characterized by pulmonary infiltrates with eosinophilia. Antineutrophil cytoplasmic antibodies (ANCA) are present in about one-third to two-thirds of patients with EGPA; binding of ANCA to vascular walls likely contributes to vascular inflammation and injury as well as chemotaxis of inflammatory cells.

ACUTE EOSINOPHILIC PNEUMONIA

Acute eosinophilic pneumonia is a syndrome characterized by fevers, acute respiratory failure that often requires mechanical ventilation,

TABLE 288-3 Diagnostic Criteria of Acute Eosinophilic Pneumonia

- Acute febrile illness with respiratory manifestations of <1 month in duration
- Hypoxemic respiratory failure
- Diffuse pulmonary infiltrates on chest x-ray
- Bronchoalveolar lavage eosinophilia >25%
- Absence of parasitic, fungal, or other infection
- Absence of drugs known to cause pulmonary eosinophilia
- Quick clinical response to corticosteroids
- Failure to relapse after discontinuation of corticosteroids

diffuse pulmonary infiltrates, and pulmonary eosinophilia in a previously healthy individual (**Table 288-3**).

Clinical Features and Etiology At presentation, acute eosinophilic pneumonia is often mistaken for acute lung injury or acute respiratory distress syndrome (ARDS), until a BAL is performed and reveals >25% eosinophils. Although the predominant symptoms of acute eosinophilic pneumonia are cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain, physical examination findings include high fevers, basilar rales, and rhonchi on forced expiration. Acute eosinophilic pneumonia most often affects males between age 20 and 40 with no history of asthma. Although no clear etiology has been identified, several case reports have linked acute eosinophilic pneumonia to recent initiation of tobacco smoking or even electronic cigarette inhalation (vaping), or exposure to other environmental stimuli including dust from indoor renovations.

In addition to a suggestive history, the key to establishing a diagnosis of acute eosinophilic pneumonia is the presence of >25% eosinophilia on BAL fluid. While lung biopsies show eosinophilic infiltration with acute and organizing diffuse alveolar damage, it is generally not necessary to proceed to biopsy to establish a diagnosis. Although patients present with an elevated white blood cell count, in contrast to other pulmonary eosinophilic syndromes, acute eosinophilic pneumonia is often not associated with peripheral eosinophilia upon presentation. However, between 7 and 30 days of disease onset, peripheral eosinophilia often occurs with mean eosinophil counts of 1700. Erythrocyte sedimentation rate (ESR), C-reactive protein, and IgE levels are high but nonspecific, whereas HRCT is always abnormal with bilateral random patchy ground-glass or reticular opacities and small pleural effusions in as many as two-thirds of patients. Pleural fluid is characterized by a high pH with marked eosinophilia.

Clinical Course and Response to Therapy Although some patients improve spontaneously, most patients require admission to an intensive care unit and respiratory support with either invasive (intubation) or noninvasive mechanical ventilation. However, what distinguishes acute eosinophilic pneumonia from both other cases of acute lung injury as well as some of the other pulmonary eosinophilic syndromes is the absence of organ dysfunction or multisystem organ failure other than respiratory failure. One of the characteristic features of acute eosinophilic pneumonia is the high degree of corticosteroid responsiveness and the excellent prognosis. Another distinguishing feature of acute eosinophilic pneumonia is that complete clinical and radiographic recovery without recurrence or residual sequelae occurs in almost all patients within several weeks of initiation of therapy.

CHRONIC EOSINOPHILIC PNEUMONIA

In contrast to acute eosinophilic pneumonia, chronic eosinophilic pneumonia is a more indolent syndrome that is characterized by pulmonary infiltrates and eosinophilia in both the tissue and blood. Most patients are female nonsmokers with a mean age of 45, and patients do not usually develop the acute respiratory failure and significant hypoxemia appreciated in acute eosinophilic pneumonia. Similar to EGPA, a majority have asthma, with many having a history of allergies.

Patients present with a subacute illness over weeks to months, with cough, low-grade fevers, progressive dyspnea, weight loss, wheezing, malaise, and night sweats, and a chest x-ray with migratory bilateral peripheral or pleural-based opacities. Although this "photographic

negative pulmonary edema" appearance on chest x-ray and chest CT is pathognomonic of chronic eosinophilic pneumonia, <25% of patients present with this finding. Other radiographic findings include atelectasis, pleural effusions, lymphadenopathy, and septal line thickening.

Almost 90% of patients have peripheral eosinophilia, with mean eosinophil counts of over 30% of total white blood cell count. BAL eosinophilia is also an important distinguishing feature with mean BAL eosinophil counts of ~60%. Both peripheral and BAL eosinophilia are very responsive to treatment with corticosteroids. Other laboratory features of chronic eosinophilic pneumonia include increased ESR, C-reactive protein, platelets, and IgE. Lung biopsy is also often not required to establish a diagnosis but may show accumulation of eosinophils and histiocytes in the lung parenchyma and interstitium, as well as cryptogenic organizing pneumonia, but with minimal fibrosis. Nonrespiratory manifestations are uncommon, but arthralgias, neuropathy, and skin and GI symptoms have all been reported; their presence may suggest EGPA or a hypereosinophilic syndrome. Another similarity is the rapid response to corticosteroids with quick resolution of peripheral and BAL eosinophilia and improvement in symptoms. In contrast to acute eosinophilic pneumonia, though, >50% of patients relapse, and many require prolonged courses of corticosteroids for months to years.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Previously known as allergic angiitis granulomatosis or Churg-Strauss syndrome, this complex syndrome is characterized by eosinophilic vasculitis that may involve multiple organ systems including the lungs, heart, skin, GI tract, and nervous system. Although EGPA is characterized by peripheral and pulmonary eosinophilia with infiltrates on chest x-ray, the primary features that distinguish EGPA from other pulmonary eosinophilic syndromes are the presence of eosinophilic vasculitis in the setting of asthma and involvement of multiple end organs (a feature it shares with hypereosinophilic syndrome). Although perceived to be quite rare, in the last few years, there has appeared to be an increased incidence of this disease, particularly in association with various asthma therapies, including leukotriene modifiers and anti-IGE therapy with omalizumab, possibly due to concurrent systemic corticosteroid withdrawal (*forme fruste* EGPA).

The primary features of EGPA include asthma, peripheral eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and presence of eosinophilic vasculitis. The mean age at diagnosis is 48 years, with a range of 14–74 years; the average length of time between diagnosis of asthma and vasculitis is 9 years. EGPA typically occurs in several phases. The prodromal phase is characterized by asthma and allergic rhinitis, and usually begins when the individual is in his or her twenties or thirties, typically persisting for many years. The eosinophilic infiltrative phase is characterized by peripheral eosinophilia and eosinophilic tissue infiltration of various organs including the lungs and GI tract. The third phase is the vasculitic phase and may be associated with constitutional signs and symptoms including fever, weight loss, malaise, and fatigue. This phasic progression supports the hypothesis that there is a pathophysiologic continuum between eosinophilic asthma, chronic eosinophilic asthma, and EGPA.

Similar to other pulmonary eosinophilic syndromes, constitutional symptoms are very common in EGPA and include weight loss of 10–20 lb, fevers, and diffuse myalgias and migratory polyarthralgias. Myositis may be present with evidence of vasculitis on muscle biopsies. In contrast to the eosinophilic pneumonias, EGPA involves many organ systems including the lungs, skin, nerves, heart, GI tract, and kidneys.

Symptoms and Clinical Manifestations • RESPIRATORY
Most EGPA patients have asthma that arises later in life and in individuals who have no family history of atopy. The asthma can often be severe, and oral corticosteroids are often required to control symptoms but may lead to suppression of vasculitic symptoms. In addition to the more common symptoms of cough, dyspnea, sinusitis, and allergic rhinitis, alveolar hemorrhage and hemoptysis may also occur.

NEUROLOGIC Over three-fourths of EGPA patients have neurologic manifestations. Mononeuritis multiplex most commonly involves the peroneal nerve, but also involves the ulnar, radial, internal popliteal, and occasionally, cranial nerves. Cerebral hemorrhage and infarction may also occur and are important causes of death. Despite treatment, neurologic sequelae often do not completely resolve.

DERMATOLOGIC Approximately half of EGPA patients develop dermatologic manifestations. These include palpable purpura, skin nodules, urticarial rashes, and livedo.

CARDIOVASCULAR Granulomas, vasculitis, and widespread myocardial damage may be found on biopsy or at autopsy, and cardiomyopathy and heart failure may be seen in up to half of all patients but are often at least partially reversible. Acute pericarditis, constrictive pericarditis, myocardial infarction, and other electrocardiographic changes all may occur. The heart is a primary target organ in EGPA, and cardiac involvement often portends a worse prognosis.

GI GI symptoms are common in EGPA and likely represent an eosinophilic gastroenteritis characterized by abdominal pain, diarrhea, GI bleeding, and colitis. Ischemic bowel, pancreatitis, and cholecystitis have also been reported in association with EGPA and usually portend a worse prognosis.

RENAL Renal involvement is more common than once thought, and ~25% of patients have some degree of renal involvement. This may include proteinuria, glomerulonephritis, renal insufficiency, and rarely, renal infarct.

Lab Abnormalities Systemic eosinophilia is the hallmark laboratory finding in patients with EGPA and reflects the likely pathogenic role that the eosinophil plays in this disease. Eosinophilia >10% is one of the defining features of this illness and may be as high as 75% of the peripheral white blood cell count. It is present at the time of diagnosis in >80% of patients, but may respond quickly (often within 24 h) to initiation of systemic corticosteroid therapy. Even in the absence of systemic eosinophilia, tissue eosinophilia may be present.

Although not specific to EGPA, ANCs are present in approximately one-third to two-thirds of patients, mostly in a perinuclear staining pattern, with specific antibodies against myeloperoxidase detected. Nonspecific lab abnormalities that may be present in patients with EGPA include a marked elevation in ESR, a normochromic normocytic anemia, an elevated IgE, hypergammaglobulinemia, and positive rheumatoid factor and antinuclear antibodies (ANA). Although BAL often reveals significant eosinophilia, this may be seen in other eosinophilic lung diseases. Similarly, PFT often reveals an obstructive defect similar to asthma.

Radiographic Features Chest x-ray abnormalities are extremely common in EGPA and consist of bilateral, nonsegmental, patchy infiltrates that often migrate and may be interstitial or alveolar in appearance. Reticulonodular and nodular disease without cavitation can be seen, as can pleural effusions and hilar adenopathy. The most common CT findings include bilateral ground-glass opacity and airspace consolidation that is predominantly subpleural. Other CT findings include bronchial wall thickening, hyperinflation, interlobular septal thickening, lymph node enlargement, and pericardial and pleural effusions. Angiography may be used diagnostically and may show signs of vasculitis in the coronary, central nervous system, and peripheral vasculature.

Treatment and Prognosis of EGPA Most patients diagnosed with EGPA have previously been diagnosed with asthma, rhinitis, and sinusitis, and have received treatment with inhaled or systemic corticosteroids. Because these agents are also the initial treatment of choice for EGPA patients, institution of these therapies in patients with EGPA who are perceived to have severe asthma may delay the diagnosis of EGPA because signs of vasculitis may be masked. Corticosteroids dramatically alter the course of EGPA: up to 50% of those who are untreated die within 3 months of diagnosis, whereas treated patients have a 6-year survival of >70%. Common causes of death include

heart failure, cerebral hemorrhage, renal failure, and GI bleeding. Recent data suggest that clinical remission may be obtained in >90% of patients treated; ~25% of those patients may relapse, often due to corticosteroid tapering, with a rising eosinophil count heralding the relapse. Myocardial, GI, and renal involvement most often portend a poor prognosis. In such cases, treatment with higher doses of corticosteroids or the addition of cytotoxic agents such as cyclophosphamide is often warranted. Although survival does not differ between those treated or untreated with cyclophosphamide, cyclophosphamide is associated with a reduced incidence of relapse and an improved clinical response to treatment. Recent studies examining the efficacy of anti-IL-5 therapy with mepolizumab compared with placebo have shown promise, indicating that mepolizumab is a safe and effective corticosteroid-sparing agent that can reduce relapses. Other therapies that have been used successfully in the management of EGPA include azathioprine, methotrexate, rituximab, omalizumab, intravenous gamma globulin, and interferon . Plasma exchange has not been shown to provide any additional benefit.

HYPEREOSINOPHILIC SYNDROMES

Hypereosinophilic syndromes (HES) constitute a heterogeneous group of disease entities manifest by persistent eosinophilia >1500 eosinophils/ μ L in association with end organ damage or dysfunction, in the absence of secondary causes of eosinophilia. In addition to familial, undefined, and overlap syndromes with incomplete criteria, the predominant HES subtypes are the myeloproliferative and lymphocytic variants. The myeloproliferative variants may have acquired genetic abnormalities, including of platelet-derived growth factor receptor (PDGFR), attributed to a constitutively activated tyrosine kinase fusion protein (Fip1L1-PDGFR) due to a chromosomal deletion on 4q12; this variant is often responsive to imatinib. Myeloproliferative HES may also be associated with mutations involving platelet-derived growth factor (PDGFR), Janus kinase 2 (JAK2), and fibroblast growth factor receptor 1 (FGFR1). Chronic eosinophilic leukemia with demonstrable cytogenetic abnormalities and/or blasts on peripheral smear is often categorized with the myeloproliferative HES. Clinical and laboratory findings in myeloproliferative HES may include dysplastic peripheral eosinophils, increased serum vitamin B₁₂, increased tryptase, anemia, thrombocytopenia, splenomegaly, bone marrow cellularity >80%, spindle-shaped mast cells, and myelofibrosis. The evaluation for lymphocytic HES includes searching for abnormal T-cell clonal populations.

Extrapulmonary Manifestations of HES More common in men than in women, HES occurs between the ages of 20 and 50 and is characterized by significant extrapulmonary involvement, including infiltration of the heart, GI tract, kidney, liver, joints, and skin. Cardiac involvement includes myocarditis and/or endomyocardial fibrosis, as well as a restrictive cardiomyopathy.

Pulmonary Manifestations of HES Similar to the other pulmonary eosinophilic syndromes, these HES are manifested by high levels of blood, BAL, and tissue eosinophilia. Lung involvement occurs in 40% of these patients and is characterized by cough and dyspnea, as well as pulmonary infiltrates. Although it is often difficult to discern the pulmonary infiltrates and effusions seen on chest x-ray from pulmonary edema resulting from cardiac involvement, CT scan findings include interstitial infiltrates, ground-glass opacities, and small nodules. HES are typically not associated with ANCA. IgE may be elevated in lymphocytic HES variants.

Course and Response to Therapy Unlike the other pulmonary eosinophilic syndromes, less than half of patients with these HES respond to corticosteroids as first-line therapy. Although other treatment options include hydroxyurea, cyclosporine, and interferon, the tyrosine kinase inhibitor imatinib has emerged as an important therapeutic option for patients with the myeloproliferative variant, particularly in individuals with the Fip1L1-PDGFR gene fusion. Anti-IL-5 therapy with mepolizumab or benralizumab also holds promise for these patients and is currently being investigated.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is an eosinophilic pulmonary disorder that occurs in response to allergic sensitization to antigens from *Aspergillus* species fungi. The predominant clinical presentation of ABPA is an asthmatic phenotype, often accompanied by cough with production of brownish plugs of mucus. ABPA has also been well described as a complication of cystic fibrosis. A workup for ABPA may be beneficial in patients who carry a diagnosis of asthma but have proven refractory to usual therapy. ABPA is a distinct diagnosis from simple asthma, characterized by prominent peripheral eosinophilia and elevated circulating levels of IgE (often >1000 IU/mL). Establishing a diagnosis of ABPA also requires establishing sensitivity to *Aspergillus* antigens by skin test reactivity and/or direct measurement of circulating specific IgE to *Aspergillus*. Positive serum precipitins for *Aspergillus* or direct measurement of circulating specific IgG to *Aspergillus* can be used as an adjunct diagnostic criterion. Central bronchiectasis is described as a classic finding on chest imaging in ABPA but is not necessary for making a diagnosis. Other possible findings on chest imaging include patchy infiltrates and evidence of mucus impaction.

Systemic glucocorticoids may be used in the treatment of ABPA that is persistently symptomatic despite the use of inhaled therapies for asthma. Courses of glucocorticoids should be tapered over 3–6 months, and their use must be balanced against the risks of prolonged steroid therapy. Antifungal agents such as itraconazole and voriconazole given over a 4-month course reduce the antigenic stimulus in ABPA and may therefore modulate disease activity in selected patients. Newer azole agents may be used as well. The use of monoclonal antibody against IgE (omalizumab) has been described in treating severe ABPA, particularly in individuals with ABPA as a complication of cystic fibrosis. Other monoclonal antibodies used in severe eosinophilic asthma, such as those targeting IL-5 (or its receptor) or targeting IL-4-receptor-alpha, may be considered as well in refractory cases.

ABPA-like syndromes have been reported as a result of sensitization to several non-*Aspergillus* species fungi. However, these conditions are substantially rarer than ABPA, which may be present in a significant proportion of patients with refractory asthma.

INFECTIOUS PROCESSES

Infectious etiologies of pulmonary eosinophilia are largely due to helminths and are of particular importance in the evaluation of pulmonary eosinophilia in tropical environments and in the developing world (Table 288-4). These infectious conditions may also be considered in recent travelers to endemic regions. Loffler syndrome refers to transient pulmonary infiltrates with eosinophilia that occurs in response to passage of helminthic larvae through the lungs, most commonly larvae of *Ascaris* species (roundworm). Symptoms are generally self-limited and may include dyspnea, cough, wheeze, and hemoptysis. Loffler syndrome may also occur in response to hookworm infection with *Ancylostoma duodenale* or *Necator americanus*. Chronic *Strongyloides stercoralis* infection can lead to recurrent respiratory symptoms with peripheral eosinophilia between flares. In immunocompromised hosts, including patients on glucocorticoids, a severe, potentially fatal, hyperinfection syndrome can result from *Strongyloides* infection. Paragonimiasis, filariasis, and visceral larval migrans can all cause pulmonary eosinophilia as well.

DRUGS AND TOXINS

A host of medications are associated with the development of pulmonary infiltrates with peripheral eosinophilia. Therefore, drug reaction must always be included in the differential diagnosis of pulmonary eosinophilia. Although the list of medications associated with pulmonary eosinophilia is ever expanding, common culprits include nonsteroidal anti-inflammatory medications and systemic antibiotics. Additionally, various and diverse environmental exposures such as particulate metals, scorpion stings, and inhalational drugs of abuse may also cause pulmonary eosinophilia. Radiation therapy for breast cancer has been linked with eosinophilic pulmonary infiltration as well. The mainstay of treatment is removal of the offending exposure, although glucocorticoids may be necessary if respiratory symptoms are severe.

TABLE 288-4 Infectious Causes of Pulmonary Eosinophilia

Löffler Syndrome
Ascaris
Hookworm
Schistosomiasis
Heavy Parasite Burden
Strongyloidiasis
Direct Pulmonary Penetration
Paragonimiasis
Visceral larval migrans
Immunologic Response to Organisms in Lungs
Filariasis
Dirofilariasis
Cystic Disease
<i>Echinococcus</i>
Cysticercosis
Other Nonparasitic
Coccidioidomycosis
Basidiobolomycosis
Paracoccidioidomycosis
Tuberculosis

Source: Adapted from P Akuthota, PF Weller: Clin Microbiol Rev 25:649, 2012.

GLOBAL CONSIDERATIONS

In the United States, drug-induced eosinophilic pneumonias are the most common cause of eosinophilic pulmonary infiltrates. A travel history or evidence of recent immigration should prompt the consideration of parasite-associated disorders. Tropical eosinophilia is usually caused by filarial infection; however, eosinophilic pneumonias also occur with other parasites such as *Ascaris* spp., *Ancylostoma* spp., *Toxocara* spp., and *Strongyloides stercoralis*. Tropical eosinophilia due to *Wuchereria bancrofti* or *Wuchereria malayi* occurs most commonly in southern Asia, Africa, and South America and is treated successfully with diethylcarbamazine. In the United States, *Strongyloides* is endemic to the southeastern and Appalachian regions.

FURTHER READING

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factors (such as smoking and genetic risk). It is often only after a careful environmental exposure history is taken that the underlying workplace or general environmental exposure is uncovered.

Why is knowledge of occupational or environmental etiology so important? Patient management and prognosis are affected significantly by such knowledge. For example, patients with occupational asthma or hypersensitivity pneumonitis often cannot be managed adequately without cessation of exposure to the offending agent. Establishment of cause may have significant legal and financial implications for a patient who no longer can work in his or her usual job. Other exposed people may be identified as having the disease or prevented from getting it. In addition, new associations between exposure and disease may be identified (e.g., nylon flock worker's lung disease and diacetyl-induced bronchiolitis obliterans).

Although the exact proportion of lung disease due to occupational and environmental factors is unknown, a large number of individuals are at risk. For example, 15–20% of the burden of adult asthma and chronic obstructive pulmonary disease (COPD) has been estimated to be due to occupational factors.

HISTORY AND EXPOSURE ASSESSMENT

The patient's history is of paramount importance in assessing any potential occupational or environmental exposure. Inquiry into specific work practices should include questions about the specific contaminants involved, the presence of visible dusts, chemical odors, the size and ventilation of workspaces, the use of respiratory protective equipment, and whether coworkers have similar complaints. The temporal association of exposure at work and symptoms may provide clues to occupation-related disease. In addition, the patient must be questioned about alternative sources of exposure to potentially toxic agents, including hobbies, home characteristics, exposure to secondhand smoke, and proximity to traffic or industrial facilities. Short-term and long-term exposures to potential toxic agents in the distant past also must be considered.

Workers in the United States have the right to know about potential hazards in their workplaces under federal Occupational Safety and Health Administration (OSHA) regulations. Employers must provide specific information about potential hazardous agents in products being used through Safety Data Sheets as well as training in personal protective equipment and environmental control procedures. However, the introduction of new processes and/or new chemical compounds may change exposure significantly, and often only the employee on the production line is aware of the change. For the physician caring for a patient with a suspected work-related illness, a visit to the work site can be very instructive. Alternatively, an affected worker can request an inspection by OSHA. If reliable environmental sampling data are available, that information should be used in assessing a patient's exposure. Because chronic diseases may result from exposure over many years, current environmental measurements should be combined with work histories to arrive at estimates of past exposure.

LABORATORY TESTS

Exposures to inorganic and organic dusts can cause interstitial lung disease that presents with a restrictive pattern and a decreased diffusing capacity (**Chap. 285**). Similarly, exposures to a number of dusts or chemical agents may result in occupational asthma or COPD that is characterized by airway obstruction. Measurement of change in forced expiratory volume in 1 s (FEV₁) before and after a working shift can be used to detect an acute bronchoconstrictive response.

The chest radiograph is useful in detecting and monitoring the pulmonary response to mineral dusts, certain metals, and organic dusts capable of inducing hypersensitivity pneumonitis. The International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses classifies chest radiographs by the nature and size of opacities seen and the extent of involvement of the parenchyma. In general, small rounded opacities are seen in silicosis or coal worker's pneumoconiosis, and small linear opacities are seen in asbestosis. Although useful for epidemiologic studies and screening large numbers of workers, the ILO system can be problematic when

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Occupational and Environmental Lung Disease

John R. Balmes

Occupational and environmental lung diseases are difficult to distinguish from those of nonenvironmental origin. Virtually all major categories of pulmonary disease can be caused by environmental agents, and environmentally related disease usually presents clinically in a manner indistinguishable from that of disease not caused by such agents. In addition, the etiology of many diseases may be multifactorial; occupational and environmental factors may interact with other

applied to an individual worker's chest radiograph. With dusts causing rounded opacities, the degree of involvement on the chest radiograph may be extensive, whereas pulmonary function may be only minimally impaired. In contrast, in pneumoconiosis causing linear, irregular opacities like those seen in asbestosis, the radiograph may lead to underestimation of the severity of the impairment until relatively late in the disease. For patients with a history of asbestos exposure, conventional computed tomography (CT) is more sensitive for the detection of pleural thickening, and high-resolution CT (HRCT) improves the detection of asbestosis.

Other procedures that may be of use in identifying the role of environmental exposures in causing lung disease include skin prick testing or specific IgE antibody titers for evidence of immediate hypersensitivity to agents capable of inducing occupational asthma (e.g., flour antigens in bakers), specific IgG precipitating antibody titers for agents capable of causing hypersensitivity pneumonitis (e.g., pigeon antigen in bird handlers), and assays for specific cell-mediated immune responses (e.g., beryllium lymphocyte proliferation testing in nuclear workers or tuberculin skin testing in health care workers). Sometimes a bronchoscopy to obtain transbronchial biopsies of lung tissue may be required for histologic diagnosis (chronic beryllium disease [CBD]). Rarely, video-assisted thoracoscopic surgery to obtain a larger sample of lung tissue may be required to determine the specific diagnosis of environmentally induced lung disease (hypersensitivity pneumonitis or giant cell interstitial pneumonitis due to cobalt exposure).

DETERMINANTS OF INHALATIONAL EXPOSURE

The chemical and physical characteristics of inhaled agents affect both the dose and the site of deposition in the respiratory tract. Water-soluble gases such as ammonia and sulfur dioxide are absorbed in the lining fluid of the upper and proximal airways and thus tend to produce irritative and bronchoconstrictive responses. In contrast, nitrogen dioxide and phosgene, which are less soluble, may penetrate to the bronchioles and alveoli in sufficient quantities to produce acute chemical pneumonitis.

Particle size of air contaminants must also be considered. Because of their settling velocities in air, particles $>10\text{--}15\ \mu\text{m}$ in diameter do not penetrate beyond the nose and throat. Particles $<10\ \mu\text{m}$ in size are deposited below the larynx. These particles are divided into three size fractions on the basis of their size characteristics and sources. Particles $\sim 2.5\text{--}10\ \mu\text{m}$ (coarse-mode fraction) contain crustal elements such as silica, aluminum, and iron. These particles mostly deposit relatively high in the tracheobronchial tree. Although the total mass of an ambient sample is dominated by these larger respirable particles, the number of particles, and therefore the surface area on which potential toxic agents can deposit and be carried to the lower airways, is dominated by particles $<2.5\ \mu\text{m}$ (fine-mode fraction). These fine particles are created primarily by the burning of fossil fuels or high-temperature industrial processes resulting in condensation products from gases, fumes, or vapors. The smallest particles, those $<0.1\ \mu\text{m}$ in size, represent the ultrafine fraction and make up the largest number of particles; they tend to remain in the airstream and deposit in the lung only on a random basis as they come into contact with the alveolar walls. If they do deposit, however, particles of this size range may penetrate into the circulation and be carried to extrapulmonary sites. New technologies create particles of this size ("nanoparticles") for use in many commercial applications. Besides the size characteristics of particles and the solubility of gases, the actual chemical composition, mechanical properties, and immunogenicity or infectivity of inhaled material determine in large part the nature of the diseases found among exposed persons.

OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

Table 289-1 provides broad categories of exposure in the workplace and diseases associated with chronic exposure in those industries.

ASBESTOS-RELATED DISEASES

Asbestos is a generic term for several different mineral silicates, including chrysotile, amosite, anthophyllite, and crocidolite. In addition to

TABLE 289-1 Categories of Occupational Exposure and Associated Respiratory Conditions

OCCUPATIONAL EXPOSURES	NATURE OF RESPIRATORY RESPONSES	COMMENT
Inorganic Dusts		
Asbestos: mining, processing, construction, ship repair	Fibrosis (asbestosis), pleural disease, cancer, mesothelioma	Virtually all new mining and construction with asbestos done in developing countries
Silica: mining, stone cutting, sandblasting, quarrying, artificial stone manufacture and installation	Fibrosis (silicosis), progressive massive fibrosis (PMF), cancer, tuberculosis, chronic obstructive pulmonary disease (COPD)	Improved protection in United States; persistent risk in developing countries
Coal dust: mining	Fibrosis (coal worker's pneumoconiosis), PMF, COPD	Risk persists in certain areas of United States, increasing in countries where new mines open
Beryllium: processing alloys for nuclear power and weapons, aerospace, and electronics	Acute pneumonitis (rare), chronic granulomatous disease, lung cancer (highly suspect)	Risk in high-tech industries persists
Other metals: aluminum, chromium, cobalt, nickel, titanium, tungsten carbide, or "hard metal" (contains cobalt)	Wide variety of conditions from acute pneumonitis to lung cancer and asthma	New diseases appear with new process development
Organic Dusts		
Cotton dust: milling, processing	Byssinosis (an asthma-like syndrome), chronic bronchitis, COPD	Increasing risk in developing countries with drop in United States as jobs shift overseas
Grain dust: elevator agents, dock workers, milling, bakers	Asthma, chronic bronchitis, COPD	Risk shifting more to migrant labor pool
Other agricultural dusts: fungal spores, vegetable products, insect fragments, animal dander, bird and rodent feces, endotoxins, microorganisms, pollens	Hypersensitivity pneumonitis (farmer's lung), asthma, chronic bronchitis	Important in migrant labor pool but also resulting from in-home exposures
Toxic chemicals: wide variety of industries; see Table 289-2	Asthma, chronic bronchitis, COPD, hypersensitivity pneumonitis, pneumoconiosis, and cancer	Reduced risk with recognized hazards; increasing risk for developing countries where controlled labor practices are less stringent
Other Environmental Agents		
Uranium and radon daughters, secondhand tobacco smoke, polycyclic aromatic hydrocarbons (PAHs), biomass smoke, diesel exhaust, welding fumes, wood finishing	Occupational exposures estimated to contribute to up to 10% of all lung cancers; chronic bronchitis, COPD, and fibrosis	In-home exposures important; in developing countries, biomass smoke is a major risk factor for COPD among women in these countries

2168 workers involved in the production of asbestos products (mining, milling, and manufacturing), many workers in the shipbuilding and construction trades, including pipe fitters and boilermakers, were occupationally exposed because asbestos was widely used during the twentieth century for its thermal and electrical insulation properties. Asbestos also was used in the manufacture of fire-resistant textiles, in cement and floor tiles, and in friction materials such as brake and clutch linings.

Exposure to asbestos is not limited to persons who directly handle the material. Cases of asbestos-related diseases have been encountered in individuals with only bystander exposure, such as painters and electricians who worked alongside insulation workers in a shipyard. Community exposure resulted from the use of asbestos-containing mine and mill tailings as landfill, road surface, and playground material (e.g., Libby, MT, the site of a vermiculite mine in which the ore was contaminated with asbestos). Finally, exposure can occur from the disturbance of naturally occurring asbestos (e.g., from increasing residential development in the foothills of the Sierra Mountains in California).

Asbestos has largely been replaced in the developed world with synthetic mineral fibers such as fiberglass and refractory ceramic fibers, but it continues to be used in the developing world. The major health effects from exposure to asbestos are pleural and pulmonary fibrosis, cancers of the respiratory tract, and pleural and peritoneal mesothelioma.

Asbestosis is a diffuse interstitial fibrotic disease of the lung that is directly related to the intensity and duration of exposure. The disease resembles other forms of diffuse interstitial fibrosis (Chap. 293). Usually, exposure has taken place for at least 10 years before the disease becomes manifest. The mechanisms by which asbestos fibers induce lung fibrosis are not completely understood but are known to involve oxidative injury due to the generation of reactive oxygen species by the transition metals on the surface of the fibers as well as from cells engaged in phagocytosis.

Past exposure to asbestos is specifically indicated by pleural plaques on chest radiographs, which are characterized by either thickening or calcification along the parietal pleura, particularly along the lower lung fields, the diaphragm, and the cardiac border. Without additional manifestations, pleural plaques imply only exposure, not pulmonary impairment. Benign pleural effusions also may occur.

Irregular or linear opacities that usually are first noted in the lower lung fields are the chest radiographic hallmark of asbestosis. An indistinct heart border or a “ground-glass” appearance in the lung fields may be seen. HRCT may show distinct changes of subpleural curvilinear lines 5–10 mm in length that appear to be parallel to the pleural surface (Fig. 289-1).

Pulmonary function testing in asbestosis reveals a restrictive pattern with a decrease in both lung volumes and diffusing capacity. There may also be evidence of mild airflow obstruction (due to peribronchiolar fibrosis).

Because no specific therapy is available for asbestosis, supportive care is the same as that given to any patient with diffuse interstitial fibrosis of any cause. In general, newly diagnosed cases will have resulted from exposures that occurred many years before.

Lung cancer (Chap. 78) is the most common cancer associated with asbestos exposure. The excess frequency of lung cancer (all histologic types) in asbestos workers is associated with a minimum latency of 15–19 years between first exposure and development of the disease. Persons with more exposure are at greater risk of disease. In addition, there is a significant interactive effect of smoking and asbestos exposure that results in greater risk than what would be expected from the additive effect of each factor.

Mesotheliomas (Chap. 294), both pleural and peritoneal, are also associated with asbestos exposure. In contrast to lung cancers, these tumors do not appear to be associated with smoking. Relatively short-term asbestos exposures of 1–2 years, occurring up to 40 years in the past, have been associated with the development of mesotheliomas (an observation that emphasizes the importance of obtaining a complete environmental exposure history). Although the risk of mesothelioma is much less than that of lung cancer among asbestos-exposed workers, ~3000 cases per year are diagnosed in the United States.

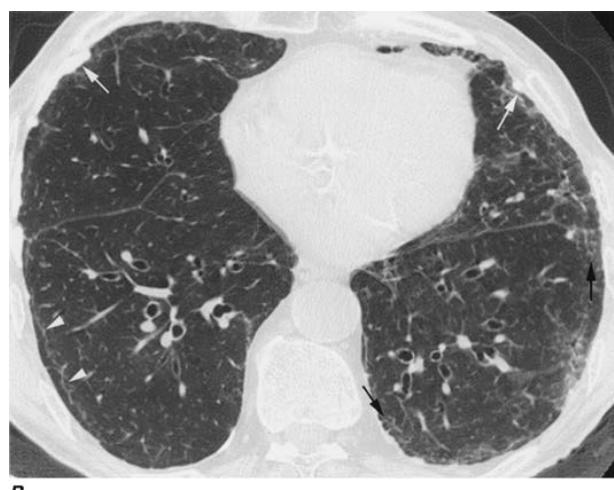
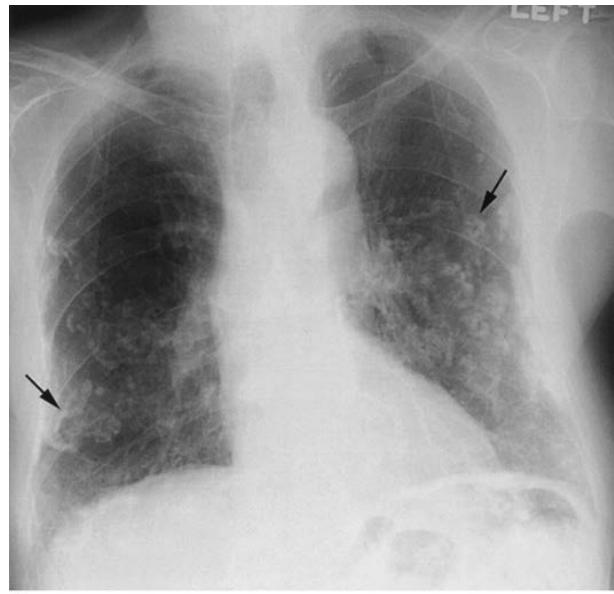


FIGURE 289-1 Asbestosis. **A.** Frontal chest radiograph shows bilateral calcified pleural plaques consistent with asbestos-related pleural disease. Poorly defined linear and reticular abnormalities are seen in the lower lobes bilaterally. **B.** Axial high-resolution computed tomography of the thorax obtained through the lung bases shows bilateral, subpleural reticulation (black arrows), representing fibrotic lung disease due to asbestosis. Subpleural lines are also present (arrowheads), characteristic of, though not specific for, asbestosis. Calcified pleural plaques representing asbestos-related pleural disease (white arrows) are also evident.

Because epidemiologic studies have shown that >80% of mesotheliomas may be associated with asbestos exposure, documented mesothelioma in a patient with occupational or environmental exposure to asbestos may be compensable.

SILICOSIS

Despite being one of the oldest known occupational pulmonary hazards, *free silica* (SiO_2), or crystalline quartz, is still a major cause of disease. The major occupational exposures include mining; stonemasonry; sand blasting; glass and cement manufacturing; foundry work; packing of silica flour; and quarrying, particularly of granite. Most often, pulmonary fibrosis due to silica exposure (silicosis) occurs in a dose-response fashion after many years of exposure. Two recent outbreaks of silicosis have involved sandblasting of denim jeans to make



FIGURE 289-2 Acute silicosis. This high-resolution computed tomography scan shows multiple small nodules consistent with silicosis but also diffuse ground-glass densities with thickened intralobular and interlobular septa producing polygonal shapes. This has been referred to as “crazy paving.”

them look “used,” and manufacture and installation of artificial stone (“faux granite”) kitchen countertops.

Workers heavily exposed through sandblasting in confined spaces, tunneling through rock with a high quartz content (15–25%), or the manufacture of abrasive soaps may develop acute silicosis with as little as 10 months of exposure. The clinical and pathologic features of acute silicosis are similar to those of pulmonary alveolar proteinosis (**Chap. 293**). The chest radiograph may show profuse miliary infiltration or consolidation, and there is a characteristic HRCT pattern known as “crazy paving” (**Fig. 289-2**). The disease may be quite severe and progressive despite the discontinuation of exposure. Whole-lung lavage may provide symptomatic relief and slow the progression.

With long-term, less intense exposure, small rounded opacities in the upper lobes may appear on the chest radiograph after 15–20 years of exposure, usually without associated impairment of lung function (*simple silicosis*). Calcification of hilar nodes may occur in as many as 20% of cases and produces a characteristic “eggshell” pattern. Silicotic nodules may be identified more readily by HRCT (**Fig. 289-3**). The nodular fibrosis may be progressive in the absence of further exposure, with coalescence and formation of nonsegmental conglomerates of irregular masses >1 cm in diameter (*complicated silicosis*). These masses can become quite large, and when this occurs, the term *progressive massive fibrosis* (PMF) is applied. Significant functional impairment with both restrictive and obstructive components may be associated with PMF.

Because silica causes alveolar macrophage dysfunction, patients with silicosis are at greater risk of acquiring lung infections that involve these cells as a primary defense (*Mycobacterium tuberculosis*, atypical mycobacteria, and fungi). Because of the increased risk of active tuberculosis, the recommended treatment of latent tuberculosis in these patients is longer. Silica has immunoadjuvant properties, and another potential clinical complication of silicosis is autoimmune connective tissue disorders such as rheumatoid arthritis and scleroderma. In addition, there are sufficient epidemiologic data that the International Agency for Research on Cancer lists silica as a probable lung carcinogen.

Other, less hazardous silicates include fuller’s earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate dusts, and cement

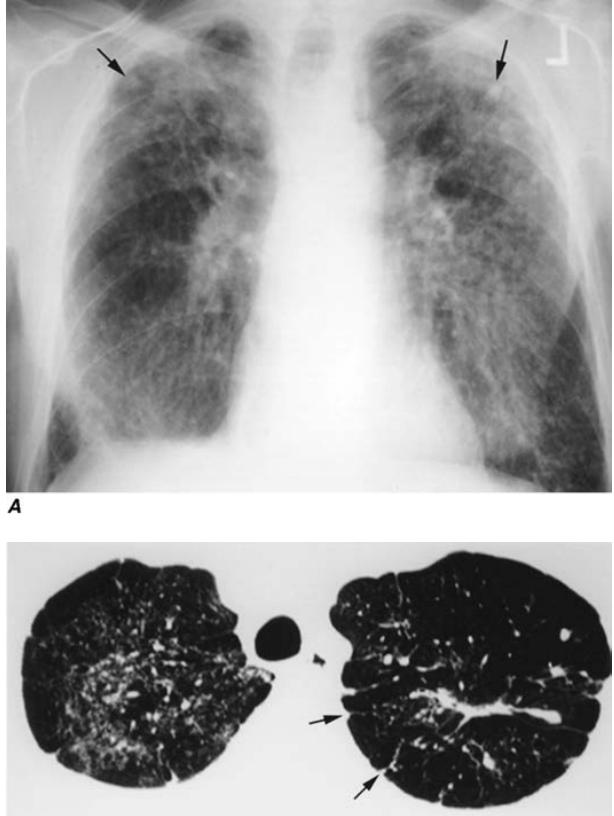


FIGURE 289-3 Chronic silicosis. **A.** Frontal chest radiograph in a patient with silicosis shows variably sized, poorly defined nodules (arrows) predominating in the upper lobes. **B.** Axial thoracic computed tomography image through the lung apices shows numerous small nodules, more pronounced in the right upper lobe. A number of the nodules are subpleural in location (arrows).

dusts. The production of fibrosis in workers exposed to these agents is believed to be related either to the free silica content of these dusts or, for substances that contain no free silica, to the potentially large dust loads to which these workers may be exposed. Some silicates, including *talc* and *vermiculite*, may be contaminated with asbestos. Fibrosis of lung or pleura, lung cancer, and mesothelioma have been associated with chronic exposure to talc and vermiculite dusts.

COAL WORKER’S PNEUMOCONIOSIS (CWP)

Occupational exposure to *coal dust* can lead to CWP, which has enormous social, economic, and medical significance in every nation in which coal mining is an important industry. Simple radiographically identified CWP is seen in ~10% of all coal miners and in as many as 50% of anthracite miners with >20 years of work on the coal face. The prevalence of disease is lower in workers in bituminous coal mines.

With prolonged exposure to coal dust (i.e., 15–20 years), small, rounded opacities similar to those of silicosis may develop. As in silicosis, the presence of these nodules (*simple CWP*) usually is not associated with pulmonary impairment. In addition to CWP, coal dust can cause chronic bronchitis and COPD (**Chap. 292**). The effects of coal dust are additive to those of cigarette smoking.

Complicated CWP is manifested by the appearance on the chest radiograph of nodules 1 cm in diameter generally confined to the upper half of the lungs. As in silicosis, this condition can progress to PMF that is accompanied by severe lung function deficits and associated with premature mortality. Despite improvements in technology to protect coal miners, cases of PMF still occur in the United States at a disturbing rate.

Caplan syndrome (Chap. 358), first described in coal miners but subsequently in patients with silicosis, is the combination of pneumoconiotic nodules and seropositive rheumatoid arthritis. Silica is often present in anthracitic coal dust, and its presence may contribute to risk of PMF.

CHRONIC BERYLLIUM DISEASE

Beryllium is a lightweight metal with tensile strength, good electrical conductivity, and value in the control of nuclear reactions through its ability to quench neutrons. Although beryllium may produce an acute pneumonitis, it is far more commonly associated with a chronic granulomatous inflammatory disease that is similar to sarcoidosis (Chap. 367). Unless one inquires specifically about occupational exposures to beryllium in the manufacture of alloys, ceramics, or high-technology electronics in a patient with sarcoidosis, one may miss entirely the etiologic relationship to the occupational exposure. What distinguishes CBD from sarcoidosis is evidence of a specific cell-mediated immune response (i.e., delayed hypersensitivity) to beryllium.

The test that usually provides this evidence is the beryllium lymphocyte proliferation test (BeLPT). The BeLPT compares the *in vitro* proliferation of lymphocytes from blood or bronchoalveolar lavage in the presence of beryllium salts with that of unstimulated cells. Proliferation is usually measured by lymphocyte uptake of radiolabeled thymidine.

Chest imaging findings are similar to those of sarcoidosis (nodules along septal lines) except that hilar adenopathy is somewhat less common. As with sarcoidosis, pulmonary function test results may show restrictive and/or obstructive ventilatory deficits and decreased diffusing capacity. With early disease, both chest imaging studies and pulmonary function tests may be normal. Fiberoptic bronchoscopy with transbronchial lung biopsy usually is required to make the diagnosis of CBD. In a beryllium-sensitized individual, the presence of noncaseating granulomas or monocytic infiltration in lung tissue establishes the diagnosis. Accumulation of beryllium-specific CD4+ T cells occurs in the granulomatous inflammation seen on lung biopsy. Susceptibility to CBD is highly associated with human leukocyte antigen DP (HLA-DP) alleles that have a glutamic acid in position 69 of the chain.

OTHER METALS

Aluminum and titanium dioxide have been rarely associated with a sarcoid-like reaction in lung tissue. Exposure to dust containing tungsten carbide, also known as “hard metal,” may produce giant cell interstitial pneumonitis. Cobalt is a constituent of tungsten carbide and is the likely etiologic agent of both the interstitial pneumonitis and the occupational asthma that may occur. The most common exposures to tungsten carbide occur in tool and dye, saw blade, and drill bit manufacture. Diamond polishing may also involve exposure to cobalt dust. In patients with interstitial lung disease, one should always inquire about exposure to metal fumes and/or dusts. Especially when sarcoidosis appears to be the diagnosis, one should always consider possible CBD.

OTHER INORGANIC DUSTS

Most of the inorganic dusts discussed thus far are associated with the production of either dust macules or interstitial fibrotic changes in the lung. Other inorganic and organic dusts (see categories in Table 289-1), along with some of the dusts previously discussed, are associated with chronic mucus hypersecretion (chronic bronchitis), with or without reduction of expiratory flow rates. Cigarette smoking is the major cause of these conditions, and any effort to attribute some component of the disease to occupational and environmental exposures must take cigarette smoking into account. Most studies suggest an additive effect of dust exposure and smoking. The pattern of the irritant dust effect is similar to that of cigarette smoking, suggesting that small airway inflammation may be the initial site of pathologic response in those cases and continued exposure may lead to chronic bronchitis and COPD.

ORGANIC DUSTS

Some of the specific diseases associated with organic dusts are discussed in detail in the chapters on asthma (Chap. 287) and hypersensitivity pneumonitis (Chap. 288). Many of these diseases are named

for the specific setting in which they are found, e.g., farmer's lung, malt worker's disease, and mushroom worker's disease. Often the temporal relation of symptoms to exposure furnishes the best evidence for the diagnosis. Three occupational exposures are singled out for discussion here because they affect the largest proportions of workers.

Cotton Dust (Byssinosis) Workers occupationally exposed to cotton dust (but also to flax, hemp, or jute dust) in the production of yarns for textiles and rope making are at risk for an asthma-like syndrome known as byssinosis. The risk of byssinosis is associated with both cotton dust and endotoxin levels in the workplace environment.

Byssinosis is characterized clinically as occasional (early-stage) and then regular (late-stage) chest tightness toward the end of the first day of the workweek (“Monday chest tightness”). Exposed workers may show a significant drop in FEV₁ over the course of a Monday workshift. Initially the symptoms do not recur on subsequent days of the week, but in a subset of workers, chest tightness may recur or persist throughout the workweek. After >10 years of exposure, workers with recurrent symptoms are more likely to have an obstructive pattern on pulmonary function testing.

Dust exposure can be reduced by the use of exhaust hoods, general increases in ventilation, and wetting procedures, but respiratory protective equipment may be required during certain operations. Regular surveillance of pulmonary function in cotton dust-exposed workers using spirometry before and after the workshift is required by OSHA. All workers with persistent symptoms or significantly reduced levels of pulmonary function should be moved to areas of lower risk of exposure.

Grain Dust Worldwide, many farmers and workers in grain storage facilities are exposed to grain dust. The presentation of obstructive airway disease in grain dust-exposed workers is virtually identical to the characteristic findings in cigarette smokers, i.e., persistent cough, mucus hypersecretion, wheeze and dyspnea on exertion, and reduced FEV₁ and FEV₁/FVC (forced vital capacity) ratio (Chap. 285).

Dust concentrations in grain elevators vary greatly but can be >10,000 µg/m³ with many particles in the respirable size range. The effect of grain dust exposure is additive to that of cigarette smoking, with ~50% of workers who smoke having symptoms. Smoking grain dust-exposed workers are more likely to have obstructive ventilatory deficits on pulmonary function testing. As in byssinosis, endotoxin may play a role in grain dust-induced chronic bronchitis and COPD.

Farmer's Lung This condition results from exposure to moldy hay containing spores of thermophilic actinomycetes that produce a hypersensitivity pneumonitis (Chap. 288). A patient with acute farmer's lung presents 4–8 h after exposure with fever, chills, malaise, cough, and dyspnea without wheezing. The history of exposure is obviously essential to distinguish this disease from influenza or pneumonia with similar symptoms. In the chronic form of the disease, the history of repeated attacks after similar exposure is important in differentiating this syndrome from other causes of patchy fibrosis (e.g., sarcoidosis).

A wide variety of other organic dusts are associated with the occurrence of hypersensitivity pneumonitis (Chap. 288). For patients who present with hypersensitivity pneumonitis, specific and careful inquiry about occupations, hobbies, and other home environmental exposures is necessary to uncover the source of the etiologic agent.

TOXIC CHEMICALS

Exposure to toxic chemicals affecting the lung generally involves gases and vapors. A common accident is one in which the victim is trapped in a confined space where the chemicals have accumulated to harmful levels. In addition to the specific toxic effects of the chemical, the victim often sustains considerable anoxia, which can play a dominant role in determining whether the individual survives.

Table 289-2 lists a variety of toxic agents that can produce acute and sometimes life-threatening reactions in the lung. All these agents in sufficient concentrations have been demonstrated, at least in animal studies, to affect the lower airways and disrupt alveolar architecture, either acutely or as a result of chronic exposure.

TABLE 289-2 Selected Common Toxic Chemical Agents That Affect the Lung

AGENT(S)	SELECTED EXPOSURES	ACUTE EFFECTS FROM HIGH OR ACCIDENTAL EXPOSURE	CHRONIC EFFECTS FROM RELATIVELY LOW EXPOSURE
Acid anhydrides	Manufacture of resin esters, polyester resins, thermoactivated adhesives	Nasal irritation, cough	Asthma, chronic bronchitis, hypersensitivity pneumonitis
Acid fumes: H_2SO_4 , HNO_3	Manufacture of fertilizers, chlorinated organic compounds, dyes, explosives, rubber products, metal etching, plastics	Mucous membrane irritation, followed by chemical pneumonitis 2–3 days later	Bronchitis and suggestion of mildly reduced pulmonary function in children with lifelong residential exposure to high levels
Acrolein and other aldehydes	By-product of burning plastics, woods, tobacco smoke	Mucous membrane irritant, decrease in lung function	Upper respiratory tract irritation
Ammonia	Refrigeration; petroleum refining; manufacture of fertilizers, explosives, plastics, and other chemicals	Same as for acid fumes, but bronchiectasis also has been reported	Upper respiratory tract irritation, chronic bronchitis
Cadmium fumes	Smelting, soldering, battery production	Mucous membrane irritant, acute respiratory distress syndrome (ARDS)	Chronic obstructive pulmonary disease (COPD)
Formaldehyde	Manufacture of resins, leathers, rubber, metals, and woods; laboratory workers, embalmers; emission from urethane foam insulation	Same as for acid fumes	Nasopharyngeal cancer
Halides and acid salts (Cl, Br, F)	Bleaching in pulp, paper, textile industry; manufacture of chemical compounds; synthetic rubber, plastics, disinfectant, rocket fuel, gasoline	Mucous membrane irritation, pulmonary edema; possible reduced forced vital capacity (FVC) 1–2 years after exposure	Upper respiratory tract irritation, epistaxis, tracheobronchitis
Hydrogen sulfide	By-product of many industrial processes, oil, other petroleum processes and storage	Increase in respiratory rate followed by respiratory arrest, lactic acidosis, pulmonary edema, death	Conjunctival irritation, chronic bronchitis, recurrent pneumonitis
Isocyanates (TDI, HDI, MDI)	Production of polyurethane foams, plastics, adhesives, surface coatings	Mucous membrane irritation, dyspnea, cough, wheeze, pulmonary edema	Upper respiratory tract irritation, cough, asthma, hypersensitivity pneumonitis, reduced lung function
Nitrogen dioxide	Silage, metal etching, explosives, rocket fuels, welding, by-product of burning fossil fuels	Cough, dyspnea, pulmonary edema may be delayed 4–12 h; possible result from acute exposure: bronchiolitis obliterans in 2–6 weeks	Emphysema in animals, chronic bronchitis, associated with reduced lung function growth in children with lifelong residential exposure
Ozone	Arc welding, flour bleaching, deodorizing, emissions from copying equipment, photochemical air pollutant	Mucous membrane irritant, reduced pulmonary function transiently in children and adults, asthma exacerbation	Excess cardiopulmonary mortality rates, increased risk for new-onset asthma in children
Phosgene	Organic compound, metallurgy, volatilization of chlorine-containing compounds	Delayed onset of bronchiolitis and pulmonary edema	Chronic bronchitis
Sulfur dioxide	Manufacture of sulfuric acid, bleaches, coating of nonferrous metals, food processing, refrigerant, burning of fossil fuels, wood pulp industry	Mucous membrane irritant, epistaxis, bronchospasm (especially in people with asthma)	Chronic bronchitis

Abbreviations: HDI, hexamethylene diisocyanate; MDI, methylene diphenyl diisocyanate; TDI, toluene diisocyanate.

Firefighters and fire victims are at risk of *smoke inhalation*, an important cause of acute cardiorespiratory failure. Smoke inhalation kills more fire victims than does thermal injury. Carbon monoxide poisoning with resulting significant hypoxemia can be life-threatening (Chap. 459). Synthetic materials (plastic, polyurethanes), when burned, may release a variety of other toxic agents (such as cyanide and hydrochloric acid), and this must be considered in evaluating smoke inhalation victims. Exposed victims may have some degree of lower respiratory tract inflammation and/or pulmonary edema.

Exposure to certain highly reactive, low-molecular-weight agents used in the manufacture of synthetic polymers, paints, and coatings (*diisocyanates* in polyurethanes, *aromatic amines* and *acid anhydrides* in epoxies) is associated with a high risk of occupational asthma. Although this occupational asthma manifests clinically as if sensitization has occurred, an IgE antibody-mediated mechanism is not necessarily involved. Hypersensitivity pneumonitis-like reactions also have been described in diisocyanate and acid anhydride-exposed workers.

Fluoropolymers such as Teflon, which at normal temperatures produce no reaction, become volatilized upon heating. The inhaled agents cause a characteristic syndrome of fever, chills, malaise, and occasionally mild wheezing, leading to the diagnosis of *polymer fume fever*. A similar self-limited, influenza-like syndrome—*metal fume fever*—results from acute exposure to fumes containing zinc oxide, typically from welding of galvanized steel. These inhalational fever syndromes may begin several hours after work and resolve within 24 h, only to return on repeated exposure.

Two other agents have been associated with potentially severe lung disease. Occupational exposure to nylon flock has been shown to induce a lymphocytic bronchiolitis, and workers exposed to diacetyl, which is used to provide “butter” flavor in the manufacture of microwave popcorn and other foods, have developed bronchiolitis obliterans (Chap. 293).

World Trade Center Disaster A consequence of the attack on the World Trade Center (WTC) on September 11, 2001, was relatively heavy exposure of a large number of firefighters and other rescue workers to the dust generated by the collapse of the buildings. Environmental monitoring and chemical characterization of WTC dust have revealed a wide variety of potentially toxic constituents, although much of the dust was pulverized cement. Possibly because of the high alkalinity of WTC dust, significant cough, wheeze, and phlegm production occurred among firefighters and cleanup crews. New cough and wheeze syndromes also occurred among local residents. Heavier exposure to WTC dust among New York City firefighters was associated with accelerated decline of lung function over the first year after the disaster. More recently, concerns have been raised about risk of interstitial lung disease, especially of a granulomatous nature.

OCCUPATIONAL RESPIRATORY CARCINOGENS

Exposures at work have been estimated to contribute to 10% of all lung cancer cases. In addition to asbestos, other agents either proven or suspected to be respiratory carcinogens include acrylonitrile, arsenic

compounds, beryllium, bis(chloromethyl) ether, chromium (hexavalent), formaldehyde (nasal), isopropanol (nasal sinuses), mustard gas, nickel carbonyl (nickel smelting), polycyclic aromatic hydrocarbons (coke oven emissions and diesel exhaust), secondhand tobacco smoke, silica (both mining and processing), talc (possible asbestos contamination in both mining and milling), vinyl chloride (sarcomas), wood (nasal), and uranium. Workers at risk of radiation-related lung cancer include not only those involved in mining or processing uranium but also those exposed in underground mining operations of other ores where radon daughters may be emitted from rock formations.

ASSESSMENT OF DISABILITY

Disability is the term used to describe the decreased ability to work due to the effects of a medical condition. Physicians are generally able to assess physiologic dysfunction, or *impairment*, but the rating of disability for compensation of loss of income also involves nonmedical factors such as the education and employability of the individual. The disability rating scheme differs with the compensation-granting agency. For example, the U.S. Social Security Administration requires that an individual be unable to do any work (i.e., *total* disability) before he or she will receive income replacement payments. Many state workers' compensation systems allow for payments for *partial* disability. In the Social Security scheme, no determination of cause is done, whereas work-relatedness must be established in workers' compensation systems.

For respiratory impairment rating, resting pulmonary function tests (spirometry and diffusing capacity) are used as the initial assessment tool, with cardiopulmonary exercise testing (to assess maximal oxygen consumption) used if the results of the resting tests do not correlate with the patient's symptoms. Methacholine challenge (to assess airway reactivity) can also be useful in patients with asthma who have normal spirometry when evaluated. Some compensation agencies (e.g., Social Security) have proscribed disability classification schemes based on pulmonary function test results. When no specific scheme is proscribed, the *Guidelines of the American Medical Association* should be used.

GENERAL ENVIRONMENTAL EXPOSURES

OUTDOOR AIR POLLUTION

Primary standards regulated by the U.S. Environmental Protection Agency (EPA) designed to protect the public health with an adequate margin of safety exist for sulfur dioxide, particulate matter (PM), nitrogen dioxide, ozone, lead, and carbon monoxide. Standards for each of these pollutants are updated regularly through an extensive review process conducted by the EPA. (For details on current standards, go to <https://www.epa.gov/criteria-air-pollutants/naaqs-table>).

Pollutants are generated from both stationary sources (power plants and industrial facilities) and mobile sources (motor vehicles), and none of the regulated pollutants occurs in isolation. Furthermore, pollutants may be changed by chemical reactions after being emitted. For example, sulfur dioxide and PM emissions from a coal-fired power plant may react in air to produce acid sulfate aerosols, which can be transported long distances in the atmosphere. Oxides of nitrogen and volatile organic compounds from automobile exhaust react with sunlight to produce ozone. Although originally recognized in Los Angeles, photochemically derived pollution ("smog") is now known to be a problem throughout the United States and in many other countries. Both acute and chronic effects of pollutant exposures have been documented in large population studies.

The symptoms and diseases associated with air pollution are the same as conditions commonly associated with cigarette smoking. In addition, decreased growth of lung function and asthma have been associated with chronic exposure to only modestly elevated levels of traffic-related air pollution. Multiple population-based time-series studies within cities have demonstrated excess health care utilization for asthma and other cardiopulmonary conditions as well as increased mortality rates. Cohort studies comparing cities that have relatively high levels of particulate exposures with less polluted communities suggest excess morbidity and mortality rates from cardiopulmonary conditions in long-term residents of the former. The strong

epidemiologic evidence that fine PM is a risk factor for cardiovascular morbidity and mortality has prompted toxicologic investigations into the underlying mechanisms. The inhalation of fine particles from combustion sources generates oxidative stress followed by local injury and inflammation in the lungs that in turn lead to autonomic and systemic inflammatory responses. Recent research findings on the health effects of air pollutants have led to stricter U.S. ambient air quality standards for ozone, oxides of nitrogen, and PM as well as greater emphasis on publicizing pollution alerts to encourage individuals with cardiovascular and respiratory disorders to stay indoors during high-pollution episodes (e.g., from wildfires).

INDOOR EXPOSURES

Secondhand tobacco smoke (**Chap. 454**), radon gas, wood smoke, and other biologic agents generated indoors must be considered. Several studies have shown that the respirable particulate load in any household is directly proportional to the number of cigarette smokers living in that home. Increases in prevalence of respiratory illnesses, especially asthma, and reduced levels of pulmonary function have been found in the children of smoking parents in a number of studies. Recent meta-analyses for lung cancer and cardiopulmonary diseases, combining data from multiple secondhand tobacco smoke epidemiologic studies, suggest an ~25% increase in relative risk for each condition, even after adjustment for major potential confounders.

Exposure to *radon* gas in homes is a risk factor for lung cancer. The main radon product (radon-222) is a gas that results from the decay series of uranium-238, with the immediate precursor being radium-226. The amount of radium in earth materials determines how much radon gas will be emitted. Levels associated with excess lung cancer risk may be present in as many as 10% of the houses in the United States. When smokers reside in the home, the problem is potentially greater, because the molecular size of radon particles allows them to attach readily to smoke particles that are inhaled. Fortunately, technology is available for assessing and reducing the level of exposure.

Other indoor exposures of concern are bioaerosols that contain antigenic material (fungi, cockroaches, dust mites, and pet danders) associated with an increased risk of atopy and asthma. Indoor chemical agents include strong cleaning agents (bleach, ammonia), formaldehyde, perfumes, pesticides, and oxides of nitrogen from gas appliances. Nonspecific responses associated with "tight-building syndrome," perhaps better termed "building-associated illness," in which no particular agent has been implicated, have included a wide variety of complaints, among them respiratory symptoms that are relieved only by avoiding exposure in the building in question. The degree to which "smells" and other sensory stimuli are involved in the triggering of potentially incapacitating psychological or physical responses has yet to be determined, and the long-term consequences of such environmental exposures are unknown.

Indoor exposure to *household air pollution* from cooking or heating with solid fuels (wood, dung, crop residues, charcoal, coal) is estimated to be responsible for ~2.7% of worldwide disability-adjusted life-years (DALYs) lost, due to acute lower respiratory infections in children, COPD and lung cancer in women, and cardiovascular disease among men. This burden of disease places exposure to household air pollution as one of the leading environmental hazards for poor health on a global scale.

Forty percent of the world's population uses solid fuel for cooking, heating, or baking. Kerosene (similar to diesel fuel) is often used for lighting and sometimes cooking. This occurs predominantly in the rural areas of developing countries. Because many families burn coal or biomass fuels in open stoves, which are highly inefficient, and inside homes with poor ventilation, women and young children are exposed on a daily basis to high levels of smoke. In these homes, 24-h mean levels of fine PM have been reported to be 2–30 times higher than the National Ambient Air Quality Standard set by the U.S. EPA.

Epidemiologic studies have consistently shown associations between exposure to biomass smoke and both chronic bronchitis and COPD. Because of increased migration to the United States from developing countries, clinicians need to be aware of the chronic respiratory effects

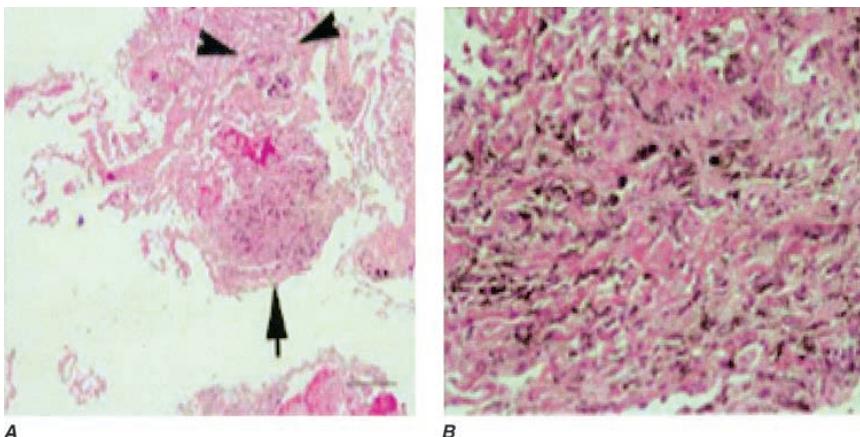


FIGURE 289-4 Histopathologic features of biomass smoke–induced interstitial lung disease. **A.** Anthracitic pigment is seen accumulating along alveolar septae (arrowheads) and within a pigmented dust macule (single arrow). **B.** A high-power photomicrograph contains a mixture of fibroblasts and carbon-laden macrophages.

of exposure to biomass smoke, which can include interstitial lung disease (Fig. 289-4). Evidence is beginning to emerge that improved stoves that reduce biomass smoke exposure can reduce risk of respiratory illness in both children and adults.

Household air pollution (HAP) from domestic use of solid fuels also contributes substantially to outdoor air pollution. Contributions from HAP, coal-fired power plants without emission scrubbers, and increased traffic congestion involving motor vehicles without pollution controls can lead to high concentrations of outdoor air pollution, especially fine PM, in mega-cities in developing countries (e.g., Delhi).

Acknowledgment

The author acknowledges the contribution of Dr. Frank Speizer to the prior version of this chapter.

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ETIOLOGY

Bronchiectasis can arise from infectious or noninfectious causes (Table 290-1). Clues to the underlying etiology often are provided by the pattern of lung involvement. *Focal bronchiectasis* refers to bronchiectatic changes in a localized area of the lung and can be a consequence of obstruction of the airway—either extrinsic (e.g., due to compression by adjacent lymphadenopathy or parenchymal tumor mass) or intrinsic (e.g., due to an airway tumor or aspirated foreign body, a scarred/stenotic airway, or bronchial atresia from congenital underdevelopment of the airway). *Diffuse bronchiectasis* is characterized by widespread bronchiectatic changes throughout the lung and often arises from an underlying systemic or infectious disease process.

More pronounced involvement of the upper lung fields is most common in CF and also is observed in postradiation fibrosis, corresponding to the lung region encompassed by the radiation port. Bronchiectasis with predominant involvement of the lower lung fields usually has its source in chronic recurrent aspiration (e.g., due to esophageal motility disorders like those in scleroderma), end-stage fibrotic lung disease (e.g., traction bronchiectasis from idiopathic pulmonary fibrosis), or recurrent immunodeficiency-associated infections (e.g., hypogammaglobulinemia). Bronchiectasis resulting from infection by nontuberculous mycobacteria (NTM), most commonly the *Mycobacterium avium-intracellulare* complex (MAC), often preferentially affects the midlung fields. Congenital causes of bronchiectasis with predominant midlung field involvement include the dyskinetic/immotile cilia syndrome. Finally, predominant involvement of the central airways is reported in association with allergic bronchopulmonary aspergillosis (ABPA), in which an immune-mediated reaction to *Aspergillus* damages the bronchial wall. Congenital causes of central airway–predominant bronchiectasis resulting from cartilage deficiency include tracheobronchomegaly (Mounier-Kuhn syndrome) and Williams-Campbell syndrome.

In many cases, the etiology of bronchiectasis is not determined. In case series, as many as 25–50% of patients referred for bronchiectasis have idiopathic disease.

EPIDEMIOLOGY

The overall reported prevalence of bronchiectasis in the United States has recently increased, but the epidemiology of bronchiectasis varies greatly with the underlying etiology. For example, patients born with CF often develop significant clinical bronchiectasis in late adolescence or early adulthood, although atypical presentations of CF in adults in their thirties and forties are also possible. In contrast, bronchiectasis resulting from MAC infection classically affects nonsmoking women >50 years of age. In general, the incidence of bronchiectasis increases with age. Bronchiectasis is more common among women than among men. Bronchiectasis may also frequently be co-diagnosed with chronic obstructive pulmonary disease (COPD) or asthma.

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Bronchiectasis

Rebecca M. Baron, Beverly W. Baron,
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Bronchiectasis refers to an irreversible airway dilation that involves the lung in either a focal or a diffuse manner and that classically has been categorized as cylindrical or tubular (the most common form), varicose, or cystic. This chapter will focus largely on non–cystic fibrosis (CF) bronchiectasis. **The reader is referred to Chapter 291 for a more focused discussion on CF bronchiectasis.**

TABLE 290-1 Major Etiologies of Bronchiectasis and Proposed Workup

PATTERN OF LUNG INVOLVEMENT	ETOLOGY BY CATEGORY (EXAMPLES)	WORKUP
Focal	Obstruction (aspirated foreign body, tumor mass)	Chest imaging (chest x-ray and/or chest CT); bronchoscopy
Diffuse	Infection (bacterial, nontuberculous mycobacterial)	Sputum Gram's stain/culture; stains/cultures for acid-fast bacilli and fungi. If no pathogen is identified, consider bronchoscopy with bronchoalveolar lavage.
	Immunodeficiency (hypogammaglobulinemia, HIV infection, bronchiolitis obliterans after lung transplantation)	Complete blood count with differential; immunoglobulin measurement; HIV testing
	Genetic causes (cystic fibrosis, Kartagener's syndrome, α_1 antitrypsin deficiency)	Measurement of chloride levels in sweat (for cystic fibrosis), α_1 antitrypsin levels; nasal or respiratory tract brush/biopsy (for dyskinetic/imotile cilia syndrome); genetic testing
Autoimmune or rheumatologic causes (rheumatoid arthritis, Sjögren's syndrome, inflammatory bowel disease); immune-mediated disease (allergic bronchopulmonary aspergillosis)	Clinical examination with careful joint exam, serologic testing (e.g., for rheumatoid factor). Consider workup for allergic bronchopulmonary aspergillosis, especially in patients with refractory asthma. ^a	
Recurrent aspiration	Test of swallowing function and general neuromuscular strength	
Miscellaneous (yellow nail syndrome, traction bronchiectasis from postradiation fibrosis or idiopathic pulmonary fibrosis)	Guided by clinical condition	
Idiopathic	Exclusion of other causes	

^aSkin testing for *Aspergillus* reactivity: measurement of serum precipitins for *Aspergillus*, serum IgE levels, serum eosinophils, etc.

In areas where tuberculosis is prevalent, bronchiectasis more frequently occurs as a sequela of granulomatous infection. Focal bronchiectasis can arise from extrinsic compression of the airway by enlarged granulomatous lymph nodes and/or from development of intrinsic obstruction as a result of erosion of a calcified lymph node through the airway wall (e.g., broncholithiasis). Especially in reactivated tuberculosis, parenchymal destruction from infection can result in areas of more diffuse bronchiectasis. Apart from cases associated with tuberculosis, an increased incidence of non-CF bronchiectasis with an unclear underlying mechanism has been reported as a significant problem in developing nations. It has been suggested that the high incidence of malnutrition in certain areas may predispose to immune dysfunction and development of bronchiectasis.

PATHOGENESIS AND PATHOLOGY

The most widely cited mechanism of infectious bronchiectasis is the “vicious cycle hypothesis,” in which susceptibility to infection and poor mucociliary clearance result in microbial colonization of the bronchial tree. Some organisms, such as *Pseudomonas aeruginosa*, exhibit a particular propensity for colonizing damaged airways and evading host defense mechanisms. Impaired mucociliary clearance can result from inherited conditions such as CF or dyskinetic cilia syndrome, and it has been proposed that a single severe infection (e.g., pneumonia caused by *Bordetella pertussis* or *Mycoplasma pneumoniae*) can result in

significant airway damage and poor secretion clearance. The presence of the microbes incites continued chronic inflammation, with consequent damage to the airway wall, continued impairment of secretions and microbial clearance, and ongoing propagation of the infectious/inflammatory cycle. Moreover, it has been proposed that mediators released directly from bacteria can interfere with mucociliary clearance.

Classic studies of the pathology of bronchiectasis from the 1950s demonstrated significant small-airway wall inflammation and larger-airway wall destruction as well as dilation, with loss of elastin, smooth muscle, and cartilage. It has been proposed that inflammatory cells in the small airways release proteases and other mediators, such as reactive oxygen species and proinflammatory cytokines, that damage the larger airway walls. Furthermore, the ongoing inflammatory process in the smaller airways results in airflow obstruction. It is thought that antiproteases, such as α_1 antitrypsin, play an important role in neutralizing the damaging effects of neutrophil elastase and in enhancing bacterial killing. Bronchiectasis and emphysema have been observed in patients with α_1 antitrypsin deficiency.

Proposed mechanisms for noninfectious bronchiectasis include immune-mediated reactions that damage the bronchial wall (e.g., those associated with systemic autoimmune conditions such as Sjögren's syndrome and rheumatoid arthritis). Recent studies suggest that there might exist a new bronchiectasis endophenotype of patients with sensitization to multiple environmental allergens. *Traction bronchiectasis* refers to dilated airways arising from parenchymal distortion as a result of lung fibrosis (e.g., postradiation fibrosis or idiopathic pulmonary fibrosis).

CLINICAL MANIFESTATIONS

The most common clinical presentation is a persistent productive cough with ongoing production of thick, tenacious sputum. Physical findings frequently include crackles and wheezing on lung auscultation, and some patients with bronchiectasis exhibit clubbing of the digits. Mild to moderate airflow obstruction often is detected on pulmonary function tests, overlapping with that seen at presentation with other conditions, such as COPD. Acute exacerbations of bronchiectasis usually are characterized by changes in the nature of sputum production, with increased volume and purulence. However, typical signs and symptoms of lung infection, such as fever and new infiltrates, may not be present.

DIAGNOSIS

The diagnosis usually is based on presentation with a persistent chronic cough and sputum production accompanied by consistent radiographic features. Although chest radiographs lack sensitivity, the presence of “tram tracks” indicating dilated airways is consistent with bronchiectasis. Chest CT is more specific for bronchiectasis and is the imaging modality of choice for confirming the diagnosis. CT findings include airway dilation (detected as parallel “tram tracks” or as the “signet-ring sign”—a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering (including the presence of tubular structures within 1 cm from the pleural surface), bronchial wall thickening in dilated airways, inspissated secretions (e.g., the “tree-in-bud” pattern), or cysts emanating from the bronchial wall (especially pronounced in cystic bronchiectasis) (Fig. 290-1).

APPROACH TO THE PATIENT

Bronchiectasis

The evaluation of a patient with bronchiectasis entails elicitation of a clinical history, chest imaging, and a workup to determine the underlying etiology. Evaluation of focal bronchiectasis almost always requires bronchoscopy to exclude airway obstruction by an underlying mass or foreign body. A workup for diffuse bronchiectasis includes analysis for the major etiologies (Table 290-1), with an initial focus on excluding CF. Pulmonary function testing is an important component of a functional assessment of the patient.

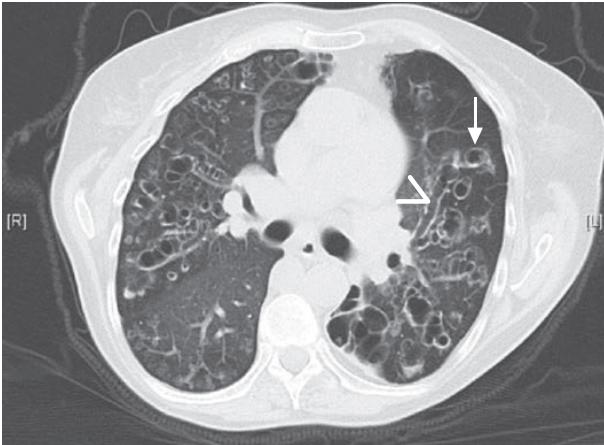


FIGURE 290-1 Representative chest CT image of severe bronchiectasis. This patient's CT demonstrates many severely dilated airways, seen both longitudinally (arrowhead) and in cross-section (arrow).

TREATMENT

Bronchiectasis

Treatment of infectious bronchiectasis is directed at the control of active infection and improvements in secretion clearance and bronchial hygiene so as to decrease the microbial load within the airways and minimize the risk of repeated infections.

ANTIBIOTIC TREATMENT

Antibiotics targeting the causative or presumptive pathogen (with *Haemophilus influenzae* and *P. aeruginosa* isolated commonly) should be administered in acute exacerbations, usually for a minimum of 7–10 days and perhaps for as long as 14 days. Decisions about treatment of NTM infection can be difficult, given that these organisms can be colonizers as well as pathogens and the prolonged treatment course often is not well tolerated. Consensus guidelines have advised that diagnostic criteria for true clinical infection with NTM should be considered in patients with symptoms and radiographic findings of lung disease who have at least two sputum samples positive on culture; at least one bronchoalveolar lavage (BAL) fluid sample positive on culture; a biopsy sample displaying histopathologic features of NTM infection (e.g., granuloma or a positive stain for acid-fast bacilli) along with one positive sputum culture; or a pleural fluid sample (or a sample from another sterile extrapulmonary site) positive on culture. MAC strains are the most common NTM pathogens, and the recommended regimen for HIV-negative patients infected with macrolide-sensitive MAC includes a macrolide combined with rifampin and ethambutol. Consensus guidelines recommend macrolide susceptibility testing for clinically significant MAC isolates.

BRONCHIAL HYGIENE

The numerous approaches used to enhance secretion clearance in bronchiectasis include hydration and mucolytic administration, aerosolization of bronchodilators and hyperosmolar agents (e.g., hypertonic saline), and chest physiotherapy (e.g., postural drainage, traditional mechanical chest percussion via hand clapping to the chest, or use of devices such as an oscillatory positive expiratory pressure flutter valve or a high-frequency chest wall oscillation vest). Pulmonary rehabilitation and a regular exercise program may assist with secretion clearance as well as with other aspects of bronchiectasis, including improved exercise capacity and quality of life. The mucolytic dornase (DNase) is recommended routinely in CF-related bronchiectasis but not in non-CF bronchiectasis, given concerns about lack of efficacy and potential harm in the non-CF population.

ANTI-INFLAMMATORY THERAPY

It has been proposed that control of the inflammatory response may be of benefit in bronchiectasis, and relatively small-scale trials have yielded evidence of alleviated dyspnea, decreased need for inhaled β -agonists, and reduced sputum production with inhaled glucocorticoids. However, no significant differences in lung function or bronchiectasis exacerbation rates have been observed. Risks of immunosuppression and adrenal suppression must be carefully considered with use of anti-inflammatory therapy in infectious bronchiectasis. Nevertheless, administration of oral/systemic glucocorticoids may be important in treatment of bronchiectasis due to certain etiologies, such as ABPA, or of noninfectious bronchiectasis due to underlying conditions, especially that in which an autoimmune condition is believed to be active (e.g., rheumatoid arthritis or Sjögren's syndrome). Patients with ABPA also may benefit from a prolonged course of treatment with the oral antifungal agent itraconazole.

REFRACTORY CASES

In select cases, surgery can be considered, with resection of a focal area of suppuration. In advanced cases, lung transplantation can be considered.

COMPLICATIONS

In more severe cases of infectious bronchiectasis, recurrent infections and repeated courses of antibiotics can lead to microbial resistance to antibiotics. In certain cases, combinations of antibiotics that have independent toxicity profiles may be necessary to treat resistant organisms.

Recurrent infections can result in injury to superficial mucosal vessels, with bleeding and, in severe cases, life-threatening hemoptysis. Management of massive hemoptysis usually requires intubation to stabilize the patient, identification of the source of bleeding, and protection of the nonbleeding lung. Control of bleeding often necessitates bronchial artery embolization and, in severe cases, surgery.

PROGNOSIS

Outcomes of bronchiectasis can vary widely with the underlying etiology and comorbid conditions and also may be influenced by the frequency of exacerbations and (in infectious cases) the specific pathogens involved (with worse outcomes associated with *P. aeruginosa* colonization). Increasing attention is being given to defining clinical subphenotypes of bronchiectasis in light of heterogeneous clinical, radiographic, and microbial features and to developing screening tools for the assessment of quality of life and disease severity. In one study, the decline of lung function in patients with non-CF bronchiectasis was similar to that in patients with COPD, with the forced expiratory volume in 1 s (FEV₁) declining by 50–55 mL per year as opposed to 20–30 mL per year for healthy controls.

PREVENTION

Reversal of an underlying immunodeficient state (e.g., by administration of gamma globulin for immunoglobulin-deficient patients) and vaccination of patients with chronic respiratory conditions (e.g., influenza and pneumococcal vaccines) can decrease the risk of recurrent infections. Patients who smoke should be counseled about smoking cessation.

After resolution of an acute infection in patients with recurrences (e.g., 3 episodes per year), the use of suppressive antibiotics to minimize the microbial load and reduce the frequency of exacerbations has been proposed. Although there is less consensus about this approach in non-CF-associated bronchiectasis than in CF-related bronchiectasis, small studies have supported benefits of selected therapies. Possible suppressive treatments include (1) administration of an oral antibiotic (e.g., ciprofloxacin) daily for 1–2 weeks per month; (2) use of a rotating schedule of oral antibiotics (to minimize the risk of development of drug resistance); (3) administration of a macrolide antibiotic (see below) daily or three times per week (with mechanisms of possible benefit related to non-antimicrobial properties, such as anti-inflammatory effects and reduction of gram-negative bacillary

biofilms); (4) inhalation of aerosolized antibiotics (e.g., tobramycin inhalation solution) for select patients on a rotating schedule (e.g., 30 days on, 30 days off), with the goal of decreasing the microbial load without eliciting the side effects of systemic drug administration; other studies examining inhaled aztreonam and inhaled ciprofloxacin formulations have shown conflicting results, suggesting there might be subpopulations of patients with bronchiectasis who might benefit from specific therapies; and (5) intermittent administration of IV antibiotics (e.g., “clean-outs”) for patients with more severe bronchiectasis and/or resistant pathogens. In relation to macrolide therapy (point 3 above), a number of double-blind, placebo-controlled, randomized trials have been published in non-CF bronchiectasis and support a benefit of long-term macrolides (6–12 months of azithromycin or erythromycin) in decreasing rates of bronchiectasis exacerbation, mucus production, and decline in lung function. However, two of these studies and a meta-analysis also reported increased macrolide resistance in commensal pathogens, dampening enthusiasm for universal use of macrolides in this setting and raising the question of whether there might be select non-CF bronchiectasis patients with higher morbidity for whom benefits of long-term macrolides might outweigh the risks of emergence of antibiotic resistance. In particular, development of macrolide-resistant NTM is a potential concern, making treatment of those pathogens much more difficult. Furthermore, patients with different patterns of microbial colonization may not all experience similar benefits with macrolide therapy. Therefore, before chronic macrolide therapy is considered, it is advisable to rule out NTM infection and carefully consider each patient’s scenario closely, obtaining an electrocardiogram to rule out a prolonged QT interval that might place the patient at increased risk of arrhythmias.

In addition, ongoing consistent attention to bronchial hygiene can promote secretion clearance and decrease the microbial load in the airways.

FURTHER READING

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characterized by copious hyperviscous and adherent secretions that obstruct small and medium-sized airways. CF respiratory secretions are exceedingly difficult to clear, and a complex bacterial flora that includes *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* (among other pathogens, see below) is routinely cultured from CF sputum. Microbiome analysis has identified dozens of other bacterial species in CF lungs, although a relationship of these less well-characterized organisms to disease progression has not been determined. Robust pulmonary inflammation in the setting of inspissated mucus and chronic bacterial infection leads to collateral tissue injury and further aggravates respiratory decline. Organisms such as *P. aeruginosa* exhibit a stereotypic mode of pathogenesis; a sentinel and early colonization event often engenders lifelong pulmonary infection by the same genetic strain. Over a period of many years, *P. aeruginosa* evolves in CF lungs to adopt a mucoid phenotype (attributable to release of alginate exoprotein) that confers selective advantage for the pathogen and poor prognosis for the host.

Pancreatic Findings The complete name of the disease, *cystic fibrosis of the pancreas*, refers to profound tissue destruction of the exocrine pancreas, with fibrotic scarring and/or fatty replacement, cyst formation, loss of acinar tissue, and ablation of normal pancreatic architecture. As in the lung, tenacious exocrine secretions (sometimes termed *concretions*) obstruct pancreatic ducts and impair production and flow of digestive enzymes to the duodenum. The sequelae of exocrine pancreatic insufficiency include chronic malabsorption, poor growth, fat-soluble vitamin insufficiency, high levels of blood immunoreactive trypsinogen (a test used in newborn screening), and loss of pancreatic islet cell mass. CF-related diabetes mellitus is a manifestation in >30% of adults with the disease and likely multifactorial in nature (attributable to progressive destruction/dysfunction of the endocrine pancreas and, in some cases, insulin resistance or other features).

Additional Organ System Damage As in CF lung and pancreas, thick and inspissated secretions compromise numerous exocrine tissues. Obstruction of intrahepatic bile ducts and parenchymal fibrosis are commonly observed in pathologic specimens, with multilobular cirrhosis in 4–15% of patients with CF and significant hepatic insufficiency as a resulting manifestation among many adults. Contents of the intestinal lumen are often difficult to excrete, leading to meconium ileus (a presentation in 10–20% of newborns with CF) or distal intestinal obstructive syndrome in older individuals. Men typically exhibit complete involution of the vas deferens and infertility (despite functioning spermatogenesis), and ~99% of males with CF are infertile. The etiology of this dramatic anatomic defect in the male genitourinary system is not understood but may represent a developmental abnormality secondary to improper epithelial secretion in the vas or associated structures. Males with CF can conceive children through in vitro fertilization. Abnormalities of female reproductive tract secretions are likely contributors to a higher incidence of infertility among women with the disease. Radiographic evidence of sinusitis occurs in most patients with CF and is associated with organisms similar to those recovered from lower airways, suggesting the sinus may serve as a reservoir for bacterial seeding.

PATHOGENESIS

Cystic Fibrosis Transmembrane Conductance Regulator CFTR is an integral membrane protein that functions as an epithelial anion channel. The ~1480-amino-acid molecule encodes a passive conduit for chloride and bicarbonate transport across plasma membranes of epithelial tissues, with direction of ion flow dependent on the electrochemical driving force. Gating of CFTR involves conformational cycling between an open and closed configuration and is augmented by hydrolysis of adenosine triphosphate (ATP). Anion flux mediated by CFTR does not involve active transport against a concentration gradient but utilizes the energy provided from ATP hydrolysis as a central feature of ion channel mechanobiology and gating.

CFTR is situated in the apical plasma membranes of acinar and other epithelial cells where it regulates the amount and composition

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Cystic Fibrosis

Eric J. Sorscher



CLINICAL FEATURES

Cystic fibrosis (CF) is an autosomal recessive exocrinopathy affecting multiple epithelial tissues. The gene product responsible for CF (the cystic fibrosis transmembrane conductance regulator [CFTR]) serves as an anion channel in the apical (luminal) plasma membranes of epithelial cells and regulates volume and composition of exocrine secretion. An increasingly sophisticated understanding of CFTR molecular genetics and membrane protein biochemistry has facilitated CF drug discovery, with a number of recently approved agents that have transformed the clinical outlook for many with the disease.

Respiratory Manifestations The major morbidity and mortality associated with CF is attributable to pulmonary compromise,

of secretion by exocrine glands. In numerous epithelia, chloride and bicarbonate release via CFTR is followed passively by flow of water through other pathways, aiding mobilization and clearance of exocrine products. Along respiratory mucosa, CFTR is necessary to provide sufficient depth of the periciliary fluid layer (PCL), allowing normal ciliary extension and mucociliary transport. CFTR-deficient airway cells exhibit depleted PCL, causing ciliary collapse and failure to clear overlying mucus (Video 291-1). In airway submucosal glands, CFTR is expressed in acini and may participate both in the formation of mucus and extrusion of glandular secretion onto the airway surface (Fig. 291-1). In other exocrine glands characterized by abrogated mucus transport (e.g., pancreatic acini and ducts, as well as bile canaliculi, and intestinal secretions), similar pathogenic mechanisms have been implicated. In these tissues, a driving force for apical chloride and/or bicarbonate secretion is believed to promote CFTR-mediated fluid and electrolyte release into the lumen, which confers proper rheology of mucins and other exocrine products. Failure of this mechanism disrupts normal hydration and transport of glandular secretion and is widely viewed as a proximate cause of obstruction, with concomitant tissue injury.

Pulmonary Inflammation and Remodeling The CF airway is characterized by an aggressive, unrelenting, neutrophilic inflammatory response with release of proteases and oxidants leading to airway remodeling and bronchiectasis. Intense pulmonary inflammation is largely driven by chronic respiratory infection. Macrophages and other cells resident in CF lungs augment elaboration of proinflammatory cytokines, which contribute to innate and adaptive immune reactivity. CFTR-dependent abnormalities of airway surface fluid composition (e.g., pH) have been reported as contributors to impaired bacterial killing in CF lungs. The role of CFTR as a direct mediator of inflammatory responsiveness and/or pulmonary remodeling represents an important and topical area of investigation.

MOLECULAR GENETICS

DNA sequencing of *CFTR* from patients (and others) worldwide has revealed >1600 allelic mutations; several hundred of these have been well characterized as disease-causing variants. Distinguishing the single nucleotide transversions or other polymorphisms with causal relevance can sometimes present a significant challenge. The CFTR2 resource (www.cftr2.org/) helps delineate gene variants with a clear etiologic role.

CFTR defects known to elicit disease are often categorized based on molecular mechanism. For example, the common F508del mutation (nomenclature denotes omission of a single phenylalanine residue [F] at CFTR position 508) leads to a folding abnormality recognized by cellular quality control pathways. CFTR encoding F508del retains partial ion channel function, but protein maturation is arrested in the endoplasmic reticulum, and CFTR fails to arrive at the plasma membrane. Instead, F508del CFTR is misrouted and undergoes endoplasmic reticulum-associated degradation via the proteasome. *CFTR* mutations that disrupt protein maturation are termed class II defects and are by far the most common genetic abnormalities. F508del alone accounts for ~70% of defective *CFTR* alleles in the United States, where ~90% of individuals with CF carry at least one F508del mutation. (See Video 291-1.)

Other gene defects include CFTR ion channels properly trafficked to the apical cell surface but unable to open and/or gate. Such channel proteins include G551D (a glycine to aspartic acid replacement at CFTR position 551), which leads to an inability to transport Cl⁻ or HCO₃⁻ (a class III abnormality). Individuals with at least one G551D allele represent ~4% of patients with CF. *CFTR* nonsense mutations such as G542X, R553X, or W1282X (premature termination codon replaces glycine, arginine, or tryptophan at positions 542, 553, or 1282, respectively) are among the common class I defects, in addition to large deletions or other major disruptions of the gene. The W1282X mutation, for example, is prevalent among individuals of Ashkenazi descent and a predominant CF genotype in Israel. Additional categories of *CFTR* mutation include defects in the ion channel pore (class IV), RNA splicing (class V), and increased plasma membrane turnover (class VI) (Fig. 291-2).

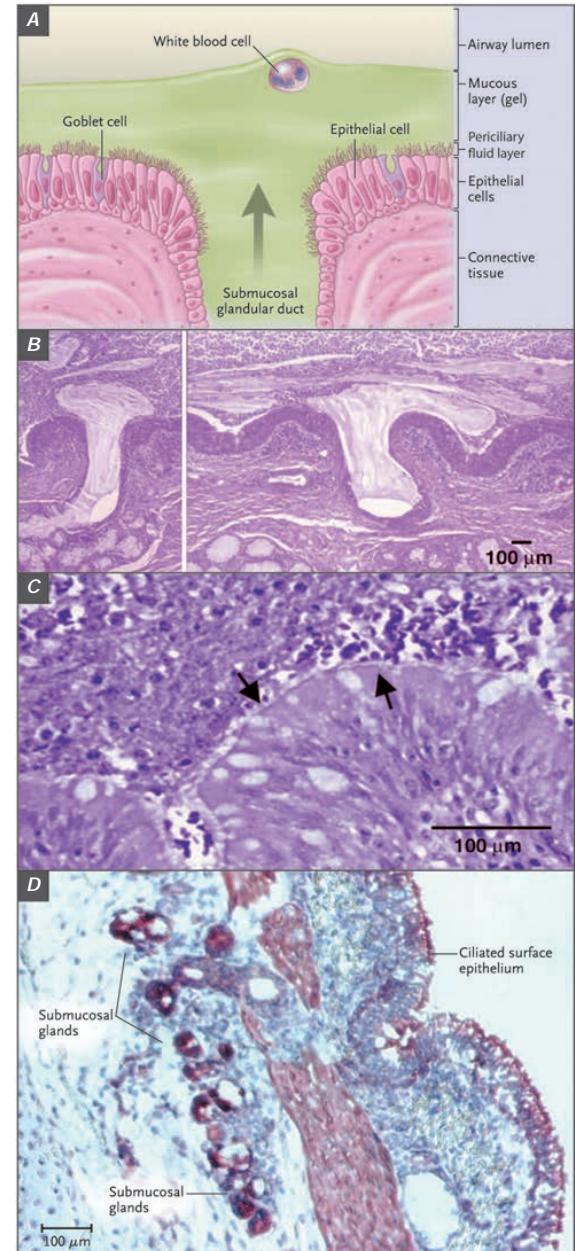


FIGURE 291-1 Extrusion of mucus secretion onto the epithelial surface of airways in cystic fibrosis (CF). **A**, Schematic of the surface epithelium and supporting glandular structure of the human airway. **B**, The submucosal glands of a patient with CF are filled with mucus, and mucopurulent debris overlies the airway surfaces, essentially burying the epithelium. **C**, A higher magnification view of a mucus plug tightly adhering to the airway surface, with arrows indicating the interface between infected and inflamed secretions and the underlying epithelium to which the secretions adhere. (Both **B** and **C** were stained with hematoxylin and eosin, with the colors modified to highlight structures.) Infected secretions obstruct airways and, over time, dramatically disrupt the normal architecture of the lung. **D**, CFTR is expressed in surface epithelium and serous cells at the base of submucosal glands in a porcine lung sample, as shown by the dark staining, signifying binding by CFTR antibodies to epithelial structures (aminoethylcarbazole detection of horseradish peroxidase with hematoxylin counterstain). (From SM Rowe, S Miller, EJ Sorscher: Cystic Fibrosis. *N Engl J Med* 352:1992, 2005. Copyright © 2005 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

DIAGNOSIS

During the past decade, newborn screening has led to most CF diagnoses, with confirmation through *CFTR* mutation analysis and sweat electrolyte measurements as cardinal tests. DNA-based

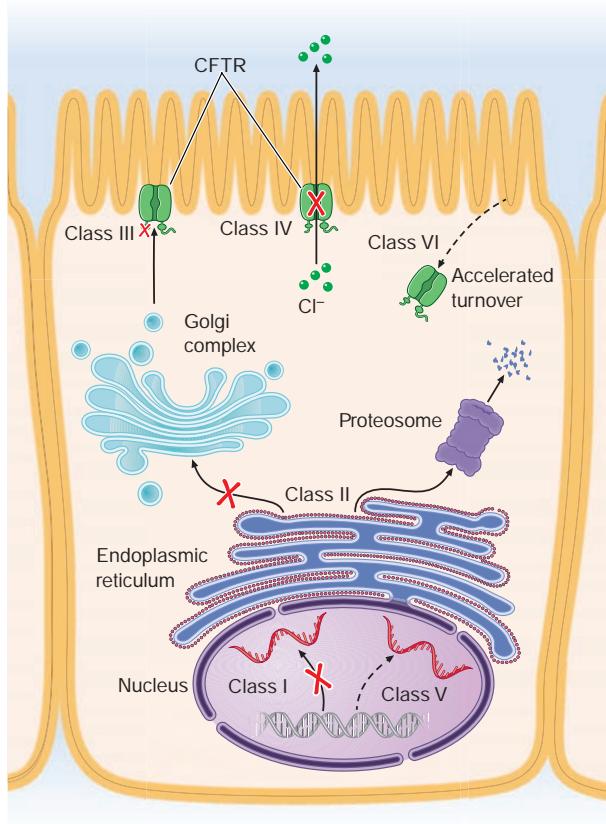


FIGURE 291-2 Categories of *CFTR* mutations. Classes of defects in the *CFTR* gene include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered gating/regulation, such as diminished adenosine triphosphate (ATP) binding and hydrolysis (class III); defective conductance through the ion channel pore (class IV); a reduced number of *CFTR* transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI). (From SM Rowe, S Miller, EJ Sorscher: *N Engl J Med* 352:1992, 2005.)

evaluation typically surveys numerous disease-associated mutations; panels that identify up to ~330 *CFTR* variants are available through a variety of public health laboratories or commercial sources. For difficult cases, complete *CFTR* exonic sequencing together with analysis of splice junctions and key regulatory elements can be obtained.

Sweat electrolytes following pilocarpine iontophoresis continue to comprise an essential diagnostic element, with levels of chloride markedly elevated in CF compared to non-CF individuals. The sweat test result is highly specific and served as a mainstay of diagnosis for many decades prior to availability of *CFTR* genotyping. Notably, hyperviscosity of eccrine sweat is not a clinical feature of the disease. Sweat ducts function to reabsorb chloride from a primary sweat secretion produced by the glandular coil. Malfunction of *CFTR* leads to diminished chloride uptake from the ductular lumen, and sweat emerges on the skin with elevated levels of chloride. For the unusual situation in which both *CFTR* genotype and sweat electrolytes are inconclusive, *in vivo* measurement of ion transport across the nasal airways can serve as a specific test for CF and is used by a number of referral centers. For example, elevated (sodium-dependent) transepithelial charge separation across airway epithelial tissue and persistent failure of isoproterenol-dependent chloride secretion (via *CFTR*) represent bioelectric findings specific for the disease. Measurements of *CFTR* activity in excised rectal mucosal biopsies can also be obtained.

COMPLEXITY OF A CF PHENOTYPE

Prior to the advent of newborn screening, CF classically presented in childhood with chronic productive cough, malabsorption including steatorrhea, and failure to thrive. The disease is most common among whites (~1 in 3300 live births) and much less frequent among African-American (~1 in 10,000) or Asian populations (~1 in 33,000). Several “severe” defects that impair *CFTR* activity (including F508del, G551D, and truncation alleles) are predictive of pancreatic insufficiency, which is clinically evident in ~90% of individuals with the disease. These few genotype-phenotype correlations notwithstanding, genotype is, in general, a poor predictor of overall respiratory prognosis.

A spectrum of *CFTR*-related conditions with features resembling classic CF has been well described. In addition to multiorgan involvement, forme frustes, such as isolated congenital bilateral absence of the vas deferens or pancreatitis (without other organ system findings), are strongly associated with *CFTR* mutations in at least one allele. Although CF is a classic monogenic disease, the importance of non-*CFTR* gene modifiers and proteins that regulate ion flux, inflammatory pathways, and airway remodeling has been appreciated as influencing clinical course. For example, the magnitude of transepithelial sodium reabsorption in CF airways, which helps control periciliary fluid depth and composition, is strongly influenced by *CFTR* and represents a molecular target for intervention.

CFTR MODULATORS

Potentiation of Mutant *CFTR* Gating A major effort directed toward high-throughput analysis of large compound libraries (including millions of individual agents) has identified effective new approaches to CF therapy. The first approved compound in this class, ivacaftor, robustly potentiates *CFTR* channel opening and stimulates ion transport. Ivacaftor overcomes the G551D *CFTR* gating defect, and individuals carrying this mutation exhibit pronounced improvement in lung function, weight gain, and other clinical benefit following oral therapy. Sweat chloride values are significantly reduced by the drug. Prior to ivacaftor, no clinical intervention of any sort had been shown to normalize the CF sweat phenotype. In addition to G551D, ivacaftor has been approved in the United States for 96 other *CFTR* variants. Multiyear administration studies indicate durable respiratory improvement. Ivacaftor has been viewed as the harbinger of a new era for CF therapeutics directed at treating the most fundamental causes of this disease.

Correction of the F508del Processing Abnormality Lumacaftor and tezacaftor, two U.S. Food and Drug Administration (FDA)-approved “corrector” molecules that repair *CFTR* misfolding (as distinct from *CFTR* gating “potentiators” such as ivacaftor), partially overcome defective F508del *CFTR* biogenesis. The drugs promote cell surface localization of F508del *CFTR*. Formulations of lumacaftor or tezacaftor (together with ivacaftor to augment channel opening) typically confer modest improvement in pulmonary function among individuals homozygous for F508del (~45% of the U.S. CF population). Elexacaftor, a next-generation corrector that operates through a different mechanism of action, is FDA-approved in combination with tezacaftor and ivacaftor for patients with CF encoding at least one F508del variant (irrespective of the other *CFTR* mutations), as well as for a series of less common *CFTR* defects. This triple combination therapy (TCT) may, therefore, benefit >90% of individuals with the disease. Marked enhancement of forced expiratory volume in 1 s (FEV₁), fewer respiratory exacerbations, improved quality of life, and diminished sweat chloride have all been demonstrated in patients following TCT, leading to designation as “highly effective modulator treatments” (HEMTs). For example, among patients carrying one F508del together with a *CFTR* minimal function variant, FEV₁ (% predicted) was improved by ~14% over a 4- to 24-week treatment period. Monitoring liver function of patients started on TCTs and attention to pharmacologic interactions, including effects mediated by CYP3A, are required. (See Video 291-2A,B.)

Personalized Molecular Therapies The advent of *CFTR* modulators with robust clinical impact has engendered new optimism regarding care of patients with CF. Based on the large number of

disease-causing *CFTR* mutations, together with the ability to group these into molecular categories (Fig. 291-2), CF has been deemed a condition ideally suited for personalized (i.e., mechanistically tailored) drug treatment. That being said, many *CFTR* variants clearly exhibit multiple molecular abnormalities (across more than one mechanistic subclass), and modulator compounds can therefore provide benefit across numerous disease subcategories. *CFTR* drug discovery—while highly successful—might, therefore, be viewed as less “personalized” or “precise” than originally envisioned. Moreover, clinical data indicate that a subset of individuals with F508del respond poorly to TCTs. Understanding the multifactorial determinants mediating favorable drug response and risk of toxicity (e.g., genomic loci other than *CFTR*, epigenetic/environmental features, complex *CFTR* alleles with numerous polymorphisms) constitutes a major objective for future research in the field.

Other Challenges Involving CF Precision Therapy The high cost of modulator compounds has often restricted third-party reimbursement to include only the specific genotypes for which FDA or other regulatory approval has been obtained. As a consequence, modulator access to potentially efficacious agents among patients with very rare *CFTR* defects, and off-label prescribing, are largely precluded. Moreover, clinical trials intended to expand the drug label can be difficult to arrange based on the small numbers of patients carrying ultra-rare alleles. *In vitro* models rigorously shown to predict clinical modulator response have proven useful in this setting (e.g., studies of primary airway or other well-validated epithelial monolayers, organoid cultures) and are being advanced as a potential means to expand regulatory approval for uncommon variants.

Progress in CF drug discovery is emblematic of what might be accomplished in other refractory inherited conditions using an approach grounded in molecular mechanism and unbiased compound library screening. Genetic manipulation (*CFTR* gene transfer, certain types of genome editing, etc.) and airway progenitor cell treatments comprise experimental strategies less dependent on a specific (i.e., personalized) *CFTR* mutation. Such approaches will require efficient, durable, and safe *in vivo* delivery, with particular emphasis on CF lung disease.

THERAPEUTICS DIRECTED TOWARD CF SEQUELAE

Chronic Outpatient Management, Including Relationship to Modulators Standard care for patients with CF is intensive, with outpatient regimens that include exogenous pancreatic enzymes taken with meals, nutritional supplementation, anti-inflammatory medication, bronchodilators, and chronic or periodic administration of oral or aerosolized antibiotics (e.g., as maintenance therapy for patients with *P. aeruginosa*). Recombinant DNase aerosols (degrade DNA strands that contribute to mucus viscosity) and nebulized hypertonic saline (serves to augment PCL depth, activate mucociliary clearance, and mobilize inspissated airway secretions) are administered routinely. Chest physiotherapy several times each day is a standard means to promote clearance of airway mucus. Among adults with CF, malabsorption, chronic inflammation, and endocrine abnormalities can lead to poor bone mineralization, requiring treatment with vitamin D, calcium, and other measures. The time, complexity, and expense of home care are considerable and take a significant toll on patients and their families.

Chronic sequelae of CF have received particular attention in the era of highly effective modulator treatment, since patients with established CF lung disease given TCT or other formulations continue to exhibit respiratory infection and inflammation despite clinical improvement. Moreover, impact of *CFTR* modulators has not been well characterized for many extrapulmonary manifestations of the disease. Improved treatments that address ongoing respiratory infection/inflammation, nutritional deficits, hepatic and endocrine abnormalities, mucostasis, or other features that persist despite modulator treatment remain a priority. Opportunities to define better these aspects of CF and simplify therapeutic regimens among patients recently started on TCT are the focus of several multicenter trials.

Pulmonary Exacerbation Severe CF respiratory exacerbation is commonly managed by hospital admission for parenteral antibiotics and frequent chest physiotherapy directed against (often multidrug-resistant) bacterial pathogens. Aggressive intervention in this setting can restore a large component of lung function, but ongoing and cumulative loss of pulmonary reserve has traditionally reflected natural history of the disease. Poor prognostic indicators such as sputum culture containing *Burkholderia cepacia* complex, mucoid *P. aeruginosa*, or atypical mycobacteria are rigorously monitored in the CF patient population. An increasing incidence of methicillin-resistant *S. aureus* has also been observed and may be associated with poor outcomes. Typical inpatient antibiotic coverage includes combination drug therapy with an aminoglycoside and -lactam for at least 14 days. Maximal improvement in lung function is often achieved by 8–10 days in that setting, although optimal duration of therapy is a subject of continuing investigation. Many families elect parenteral antibiotic treatment at home, but additional studies are needed to evaluate specific drug combinations, duration of therapy, and home versus inpatient management. Other CF respiratory sequelae that may require hospitalization include hemoptysis and pneumothorax. Hypersensitivity to *Aspergillus* (allergic bronchopulmonary aspergillosis) occurs in ~5% of individuals with the disease and should be considered in the absence of favorable response to aggressive inpatient treatment. Contributions of viral infection (including SARS-CoV-2) during acute CF respiratory decline represent an area of intense clinical interest.

Lung Transplantation For end-stage CF pulmonary failure, transplantation is a viable therapeutic option with median survival >9 years among adults with the disease. Determining optimal timing for surgery presents a substantial challenge in patients with severe respiratory compromise, particularly since the rate of continued functional decline, as well as individualized mortality risk from transplantation, can be difficult to predict. FEV₁ measurements <30% predicted, together with an assortment of other clinical parameters (hospitalization frequency, need for supplemental oxygen, etc.), are employed as thresholds for transplant referral, although patients with conditions such as significant pulmonary hypertension may merit consultation at higher FEV₁. Based on clinical outcome and other features, eligible patients with CF and their families sometimes do not pursue a surgical option. The decision is best approached through early discussions with health care providers specializing in both CF clinical management and transplantation.

CF QUALITY IMPROVEMENT

As a direct result of advances in basic research, modulator and other therapies are transforming CF from a disease that historically led to death in early childhood to a condition with frequent survival well into the fourth decade of life and beyond. Although initiating modulator treatment in young children may extend longevity even further by forestalling pulmonary damage, this prediction will require formal evaluation. As modulatory therapies advance, carefully standardized approaches to management will be essential. Well-defined protocols for CF care have been widely established, including thresholds for hospital admission, antibiotic regimens, nutritional guidelines, periodicity of diagnostic tests, and other clinical parameters. These recommendations are accepted throughout specialized CF care centers and other accredited programs. Such measures have led to markedly improved pulmonary function, weight gain, body mass index, and other clinical endpoints among patients with the disease. The same approach is expected to optimize benefit attributable to *CFTR* modulation. Standardized protocols for CF therapy can be accessed at www.cff.org/treatments/cfcareguidelines/ or through a number of excellent reviews.

GLOBAL CONSIDERATIONS

Newborn screening for CF is universal throughout the United States and Canadian provinces, Australia, New Zealand, and much of Europe, and facilitates early intervention. Nutritional and other therapies at a young age are expected to promote quality of life and increase longevity. Global implementation of quality improvement measures and access to novel therapeutics have become increasing imperatives. For

example, median survival among individuals with CF is <30 years in much of Latin America (compared to >45 years in the United States). The less favorable prognosis is attributable in part to lack of widespread diagnostic capabilities (i.e., newborn screening, sweat testing, and genetic analysis tailored to ethnic background), together with insufficient access to leading-edge, interdisciplinary treatment. Efforts to apply state-of-the-art management to underdiagnosed and underserved CF patient populations will help improve outcomes and mitigate CF health disparities in the future.

FURTHER READING

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VIDEO 291-1 Role of CFTR during airway mucociliary clearance. Initial video sequences depict establishment of the normal periciliary fluid layer bathing the surface airway epithelium, with spheres representing chloride and bicarbonate ions secreted through CFTR and across the apical (mucosal) respiratory surface. Later video describes failure of CFTR anion transport and resulting depletion of the periciliary layer, "plastering" of cilia against the mucosal surface, and accumulation of mucus in the airway with resulting bacterial infection. (Reproduced with permission from Cystic Fibrosis Foundation.)

VIDEO 291-2AB Pharmacologic modulation of mutant CFTR. Initial video (**A**) illustrates CFTR encoding an ion transport gating (class III) defect. The CF gene product is localized to the plasma membrane but incapable of conducting anions (*yellow spheres*) until a potentiator molecule (shown in *green*) binds and facilitates channel opening. Later video (**B**) describes CFTR encoding a maturational processing (protein biogenesis, class II) defect. The mutant protein is misfolded, fails to traffic to the cell surface, and is degraded by the proteasome. Binding of corrector molecules (*red spheres*) improves folding and facilitates CFTR stabilization and cell surface localization/function. (*Reproduced with permission from Cystic Fibrosis Foundation.*)

by destruction of the lung alveoli with air space enlargement; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and/or *small airway disease*, a condition in which small bronchioles are narrowed and reduced in number. The *classic definition* of COPD requires the presence of chronic airflow obstruction, determined by spirometry, that usually occurs in the setting of noxious environmental exposures—most commonly products of combustion, cigarette smoking in the United States, and biomass fuels in some other countries. Host factors such as abnormal lung development and genetics can lead to COPD. Emphysema, chronic bronchitis, and small airway disease are present in varying degrees in different COPD patients. Patients with a history of cigarette smoking without chronic airflow obstruction may have chronic bronchitis, emphysema, and dyspnea. Although these patients are not included within the classic definition of COPD, they may have similar disease processes. Respiratory symptoms and other features of COPD can occur in subjects who do not meet a definition of COPD based only on airflow obstruction determined by spirometric population thresholds of normality. Investigators in the COPDGene study recently proposed a multidimensional approach to COPD diagnosis, which is based on domains of environmental exposures, respiratory symptoms, imaging abnormalities, and physiologic abnormalities.

COPD is the fourth leading cause of death and affects >10 million persons in the United States. COPD is also a disease of increasing public health importance around the world. Globally, there are an estimated 250 million individuals with COPD.

PATHOGENESIS

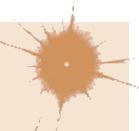
Airflow obstruction, the physiologic marker of COPD, can result from airway disease and/or emphysema. Small airways may become narrowed by cells (hyperplasia and accumulation), mucus, and fibrosis, and extensive small airway destruction has been demonstrated to be a hallmark of COPD. Although the precise biological mechanisms leading to COPD have not been determined, a number of key cell types, molecules, and pathways have been identified from cell-based and animal model studies. The pathogenesis of emphysema (shown in Fig. 292-1) is more clearly defined than the pathogenesis of small airway disease. Pulmonary vascular destruction occurs in concert with small airway disease and emphysema.

The current dominant paradigm for the pathogenesis of emphysema comprises a series of four interrelated events: (1) Chronic exposure to cigarette smoke in genetically susceptible individuals triggers inflammatory and immune cell recruitment within large and small airways and in the terminal air spaces of the lung. (2) Inflammatory cells release proteinases that damage the extracellular matrix supporting airways, vasculature, and gas exchange surfaces of the lung. (3) Structural cell death occurs through oxidant-induced damage, cellular senescence, and proteolytic loss of cellular-matrix attachments leading to extensive loss of smaller airways, vascular pruning, and alveolar destruction. (4) Disordered repair of elastin and other extracellular matrix components contributes to air space enlargement and emphysema.

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

Elastin, the principal component of elastic fibers, is a highly stable component of the extracellular matrix that is critical to the integrity of the lung. The elastase:antielastase hypothesis, proposed in the mid-1960s, postulated that the balance of elastin-degrading enzymes and their inhibitors determines the susceptibility of the lung to destruction, resulting in air space enlargement. This hypothesis was based on the clinical observation that patients with genetic deficiency in antitrypsin (α_1 AT), the inhibitor of the serine proteinase neutrophil elastase, were at increased risk of emphysema, and that instillation of elastases, including neutrophil elastase, into experimental animals results in emphysema. The elastase:antielastase hypothesis remains a prevailing mechanism for the development of emphysema. However, a complex network of immune and inflammatory cells and additional biological mechanisms that contribute to emphysema have subsequently been identified. Upon exposure to oxidants from cigarette smoke, lung

**Edwin K. Silverman, James D. Crapo,
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Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent respiratory symptoms and airflow obstruction (<https://goldcopd.org/2021-gold-reports/>). COPD includes **emphysema**, an anatomically defined condition characterized

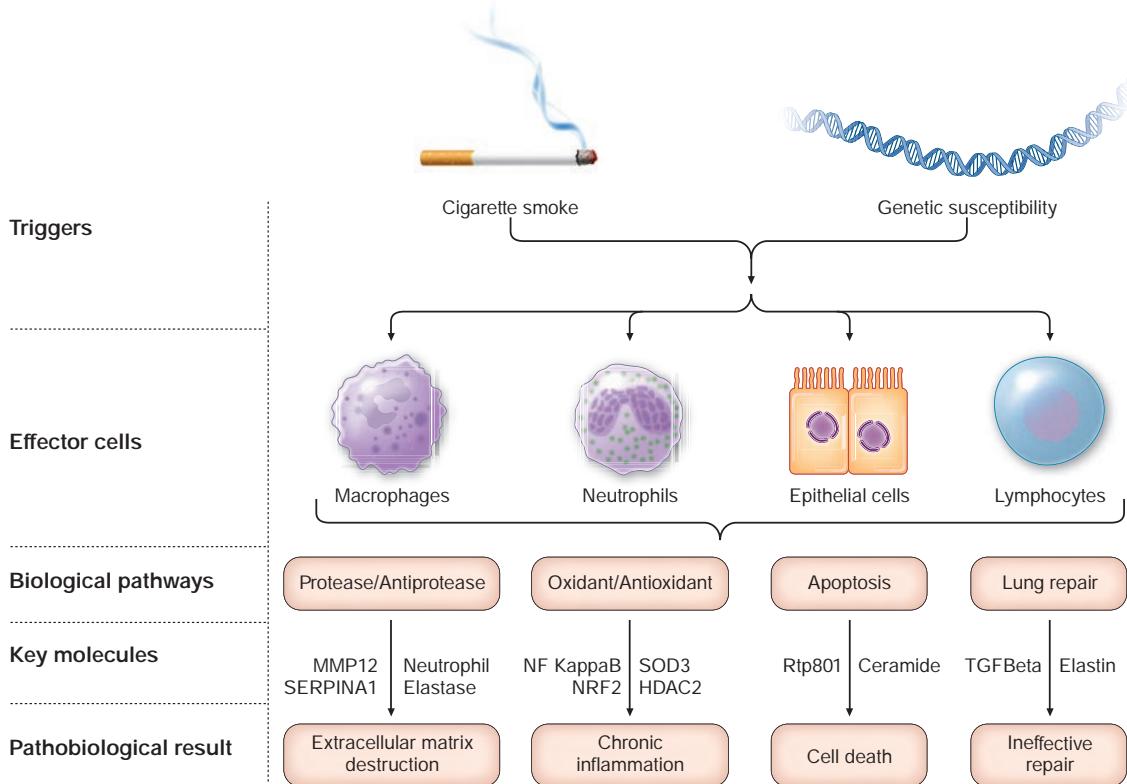


FIGURE 292-1 Pathogenesis of emphysema. Upon long-term exposure to cigarette smoke in genetically susceptible individuals, lung epithelial cells and T and B lymphocytes recruit inflammatory cells to the lung. Biological pathways of protease-antiprotease imbalance, oxidant/antioxidant imbalance, apoptosis, and lung repair lead to extracellular matrix destruction, cell death, chronic inflammation, and ineffective repair. Although most of these biological pathways influence multiple pathobiological results, only a single relationship between pathways and results is shown. A subset of key molecules related to these biological pathways is listed.

macrophages and epithelial cells become activated, producing proteinases and chemokines that attract other inflammatory and immune cells. Oxidative stress is a key component of COPD pathobiology; the transcription factor NRF2, a major regulator of oxidant-antioxidant balance, and SOD3, a potent antioxidant, have been implicated in emphysema pathogenesis by animal models. Mitochondrial dysfunction in COPD may worsen oxidative stress. One mechanism of macrophage activation occurs via oxidant-induced inactivation of histone deacetylase-2 (HDAC2), shifting the balance toward acetylated or open chromatin, exposing nuclear factor- κ B sites, and resulting in transcription of matrix metalloproteinases and proinflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor- α (TNF- α); this leads to neutrophil recruitment. CD8+ T cells are also recruited in response to cigarette smoke and release interferon-inducible protein-10 (IP-10, CXCL-7), which in turn leads to macrophage production of macrophage elastase (matrix metalloproteinase-12 [MMP-12]).

Matrix metalloproteinases and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin serve as a macrophage chemokine, and proline-glycine-proline (generated by proteolytic cleavage of collagen) is a neutrophil chemokine—fueling this destructive positive feedback loop. Elastin degradation and disordered repair are thought to be primary mechanisms in the development of emphysema.

There is some evidence that autoimmune mechanisms may promote the progression of disease. Increased B cells and lymphoid follicles are present around the airways of COPD patients, particularly those with advanced disease. Antibodies have been found against elastin fragments as well; IgG autoantibodies with avidity for pulmonary epithelium and the potential to mediate cytotoxicity have been detected.

Concomitant cigarette smoke-induced loss of cilia in the airway epithelium and impaired macrophage phagocytosis predispose to

bacterial infection with neutrophilia. In end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory response, suggesting that cigarette smoke-induced inflammation both initiates the disease and, in susceptible individuals, establishes a chronic process that can continue disease progression even after smoking cessation.

Cell Death Cigarette smoke oxidant-mediated structural cell death occurs via a variety of mechanisms including excessive ceramide production and Rtp801 inhibition of mammalian target of rapamycin (mTOR), leading to cell death as well as inflammation and proteolysis. Involvement of mTOR and other cellular senescence markers has led to the concept that emphysema resembles premature aging of the lung. Heterozygous gene-targeting of one of the leading genetic determinants of COPD identified by genome-wide association studies (GWAS), hedgehog interacting protein (*HHIP*), in a murine model leads to aging-related emphysema.

Ineffective Repair The ability of the adult lung to replace lost smaller airways and microvasculature and to repair damaged alveoli appears limited. Uptake of apoptotic cells by macrophages normally results in production of growth factors and dampens inflammation, promoting lung repair. Cigarette smoke impairs macrophage uptake of apoptotic cells, limiting repair. It is unlikely that the intricate and dynamic process of septation that is responsible for alveologenesis during lung development can be reinitiated in the adult human lung.

PATHOLOGY

Cigarette smoke exposure may affect the large airways, small airways (< 2 mm diameter), and alveoli. Changes in large airways cause cough and sputum production, while changes in small airways and alveoli are responsible for physiologic alterations. Airway inflammation,

TABLE 292-1 GOLD Criteria for Severity of Airflow Obstruction in COPD

GOLD STAGE	SEVERITY	SPIROMETRY
I	Mild	FEV ₁ /FVC <0.7 and FEV ₁ , 80% predicted
II	Moderate	FEV ₁ /FVC <0.7 and FEV ₁ , 50% but <80% predicted
III	Severe	FEV ₁ /FVC <0.7 and FEV ₁ , 30% but <50% predicted
IV	Very severe	FEV ₁ /FVC <0.7 and FEV ₁ , <30% predicted

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Source: Reproduced with permission from the Global Strategy for Diagnosis, Management and Prevention of COPD 2021, ©.

destruction, and the development of emphysema are present in most persons with COPD; however, they appear to be relatively independent processes, and their relative contributions to obstruction vary from one person to another. The early stages of COPD, based on the severity of airflow obstruction (Table 292-1), appear to be primarily associated with medium and small airway disease with the majority of Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric airflow obstruction stage 1 and stage 2 subjects demonstrating little or no emphysema. The early development of chronic airflow obstruction is driven by small airway disease. Advanced stages of COPD (GOLD stages 3 and 4) are typically characterized by extensive emphysema, although there are a small number of subjects with very severe (GOLD stage 4) obstruction with virtually no emphysema. The subjects at greatest risk of progression in COPD are those with both aggressive airway disease and emphysema. Thus, finding emphysema (by chest computed tomography [CT]) either early or late in the disease process suggests enhanced risk for disease progression.

LARGE AIRWAYS

Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production that define chronic bronchitis, but these abnormalities are not directly related to airflow obstruction. In response to cigarette smoking, goblet cells increase not only in number but also in extent through the bronchial tree. Bronchi also undergo squamous metaplasia, predisposing to carcinogenesis and disrupting mucociliary clearance. Although not as prominent as in asthma, patients may have smooth-muscle hypertrophy and bronchial hyperreactivity leading to airflow obstruction. Neutrophil influx has been associated with purulent sputum during respiratory tract infections. Independent of its proteolytic activity, neutrophil elastase is among the most potent secretagogues identified.

SMALL AIRWAYS

The major site of increased resistance in most individuals with COPD is in airways 2 mm diameter. Characteristic cellular changes include goblet cell metaplasia, with these mucus-secreting cells replacing surfactant-secreting Club cells. Smooth-muscle hypertrophy may also be present. Luminal narrowing can occur by fibrosis, excess mucus, edema, and cellular infiltration. Reduced surfactant may increase surface tension at the air-tissue interface, predisposing to airway narrowing or collapse. Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may cause proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts where the fibers are concentrated as rings around

alveolar entrances. Narrowing and drop-out of small airways precede the onset of emphysematous destruction. Advanced COPD has been shown to be associated with a loss of many of the smaller airways and a similar significant loss of the lung microvasculature.

LUNG PARENCHYMA

Emphysema is characterized by destruction of gas-exchanging air spaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli. Large numbers of macrophages accumulate in respiratory bronchioles of essentially all smokers. Neutrophils, B lymphocytes, and T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers. Alveolar walls become perforated and later obliterated with coalescence of the delicate alveolar structure into large emphysematous air spaces.

Emphysema is classified into distinct pathologic types, which include centrilobular, panlobular, and paraseptal (Fig 292-2). *Centrilobular emphysema*, the type most frequently associated with cigarette smoking, is characterized by enlarged air spaces found (initially) in association with respiratory bronchioles. Centrilobular emphysema is usually most prominent in the upper lobes and superior segments of lower lobes and is often quite focal. *Panlobular emphysema* refers to abnormally large air spaces evenly distributed within and across acinar units. Panlobular emphysema is commonly observed in patients with α_1 -AT deficiency, which has a predilection for the lower lobes. Paraseptal emphysema occurs in 10–15% of cases and is distributed along the pleural margins with relative sparing of the lung core or central regions. It is commonly associated with significant airway inflammation and with centrilobular emphysema.

PATHOPHYSIOLOGY

Persistent reduction in forced expiratory flow rates is the classic definition of COPD. Hyperinflation with increases in the residual volume and the residual volume/total lung capacity ratio, nonuniform distribution of ventilation, and ventilation-perfusion mismatching also occur.

AIRFLOW OBSTRUCTION

Airflow obstruction, also known as airflow limitation, is typically determined for clinical purposes by spirometry, which involves maximal forced expiratory maneuvers after the subject has inhaled to total lung capacity. Key parameters obtained from spirometry include the volume of air exhaled within the first second of the forced expiratory maneuver (FEV₁) and the total volume of air exhaled during the entire spirometric maneuver (forced vital capacity [FVC]). Patients with airflow obstruction related to COPD have a chronically reduced ratio of FEV₁/FVC. In contrast to asthma, the reduced FEV₁ in COPD seldom shows large improvements to inhaled bronchodilators, although improvements up to 15% are common.

HYPERTINFLATION

Lung volumes are also routinely assessed in pulmonary function testing. In COPD, there is often “air trapping” (increased residual volume and increased ratio of residual volume to total lung capacity)

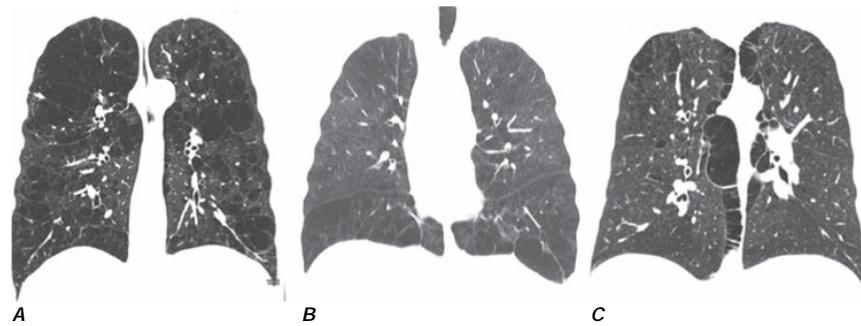


FIGURE 292-2 CT patterns of emphysema. **A.** Centrilobular emphysema with severe upper lobe involvement in a 68-year-old man with a 70-pack-year smoking history but forced expiratory volume in 1 s (FEV₁) 81% predicted (GOLD spirometry grade 1). **B.** Panlobular emphysema with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α_1 -antitrypsin (α_1 -AT) deficiency. **C.** Paraseptal emphysema with marked airway inflammation in a 52-year-old woman with a 37-pack-year smoking history and FEV₁ 40% predicted.

and progressive hyperinflation (increased total lung capacity) in more advanced disease. Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow, because as lung volume increases, elastic recoil pressure increases, and airways enlarge so that airway resistance decreases.

Despite compensating for airway obstruction, hyperinflation can push the diaphragm into a flattened position with a number of adverse effects. First, by decreasing the zone of apposition between the diaphragm and the abdominal wall, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration. Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, they are less capable of generating inspiratory pressures than normal. Third, the flattened diaphragm must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing. Fourth, the thoracic cage is distended beyond its normal resting volume, and during tidal breathing, the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume.

GAS EXCHANGE

Although there is considerable variability in the relationships between the FEV₁ and other physiologic abnormalities in COPD, certain generalizations may be made. The partial pressure of oxygen in arterial blood Pao₂ usually remains near normal until the FEV₁ is decreased to below 50% of predicted, and even much lower FEV₁ values can be associated with a normal Pao₂, at least at rest. An elevation of arterial level of carbon dioxide (Paco₂) is not expected until the FEV₁ is <25% of predicted and even then may not occur. Pulmonary arterial hypertension severe enough to cause cor pulmonale and right ventricular failure due to COPD typically occurs in individuals who have marked decreases in FEV₁ (<25% of predicted) and chronic hypoxemia (Pao₂ <55 mmHg); however, some patients develop significant pulmonary arterial hypertension independent of COPD severity (Chap. 283).

Nonuniform ventilation and ventilation-perfusion mismatching are characteristic of COPD, reflecting the heterogeneous nature of the disease process within the airways and lung parenchyma. Physiologic studies are consistent with multiple parenchymal compartments having different rates of ventilation due to regional differences in compliance and airway resistance. Ventilation-perfusion mismatching accounts for essentially all of the reduction in Pao₂ that occurs in COPD; shunting is minimal. This finding explains the effectiveness of modest elevations of inspired oxygen in treating hypoxemia due to COPD and therefore the need to consider problems other than COPD when hypoxemia is difficult to correct with modest levels of supplemental oxygen.

RISK FACTORS

CIGARETTE SMOKING

By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Subsequent longitudinal studies have shown accelerated decline in FEV₁ in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking). This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts, at least in part, for the higher prevalence rates of COPD with increasing age. The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males; however, the prevalence of COPD among females is increasing as the gender gap in smoking rates has diminished in the past 50 years.

Although the causal relationship between cigarette smoking and the development of COPD has been absolutely proved, there is considerable individual variability in the response to smoking. Pack-years of cigarette smoking is the most highly significant predictor of FEV₁ (Fig. 292-3), but only 15% of the variability in FEV₁ is explained by

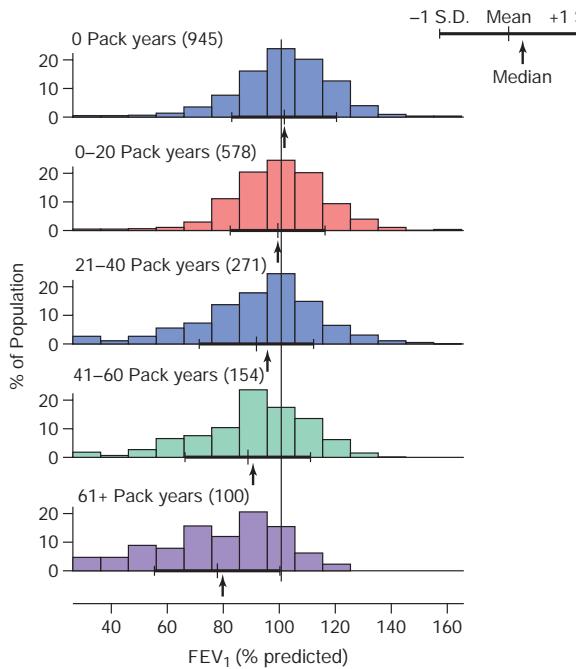


FIGURE 292-3 Distributions of forced expiratory volume in 1 s (FEV₁) values in a general population sample, stratified by pack-years of smoking. Means, medians, and ± 1 standard deviation of percent predicted FEV₁ are shown for each smoking group. Although a dose-response relationship between smoking intensity and FEV₁ was found, marked variability in pulmonary function was observed among subjects with similar smoking histories. S.D., standard deviation. (Reproduced with permission from B Burrows: Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 115:195, 1997.)

pack-years. This finding suggests that additional environmental and/or genetic factors contribute to the impact of smoking on the development of chronic airflow obstruction. Nonetheless, many patients with a history of cigarette smoking with normal spirometry have evidence for worse health-related quality of life, reduced exercise capacity, and emphysema and/or airway disease on chest CT evaluation; thus, they have not escaped the harmful effects of cigarette smoking. While they do not meet the classic definition of COPD based on population normals for FEV₁ and FEV₁/FVC, studies have shown that these subjects overall have a shift toward lower FEV₁ values, which is consistent with obstruction on an individual level.

Although cigar and pipe smoking may also be associated with the development of COPD, the evidence supporting such associations is less compelling, likely related to the lower dose of inhaled tobacco by-products during cigar and pipe smoking. The impact of electronic cigarettes and vaping on the development and progression of COPD has not yet been determined.

AIRWAY RESPONSIVENESS AND COPD

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine, is one of the defining features of asthma (Chap. 287). However, many patients with COPD also share this feature of airway hyperresponsiveness. In older subjects, there is considerable overlap between persons with a history of chronic asthma and smokers with COPD in terms of airway responsiveness, airflow obstruction, and pulmonary symptoms. The origin of asthma is viewed in many patients as an allergic disease while COPD is thought to primarily result from smoking-related inflammation and damage; however, they likely share common environmental and genetic factors and the chronic form in older subjects can present similarly. This is particularly relevant for childhood asthmatic subjects who become chronic smokers.

Longitudinal studies that compared airway responsiveness to subsequent decline in pulmonary function have demonstrated that increased

2184 airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. A study from the Childhood Asthma Management Program identified four lung function trajectories in children with persistent asthma. Asthmatics with reduced lung function early in life were more likely to meet spirometric criteria for COPD in early adulthood. Both asthma and airway hyperresponsiveness are risk factors for COPD.

RESPIRATORY INFECTIONS

The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pulmonary function are not typically seen following an individual episode of acute bronchitis or pneumonia. However, respiratory infections are important causes of COPD exacerbations, and recent results from the COPDGene and ECLIPSE studies suggest that COPD exacerbations are associated with increased loss of lung function longitudinally, particularly among those individuals with better baseline lung function levels. The impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess due to a lack of adequate longitudinal data, but recent studies have suggested that childhood pneumonia may lead to increased risk for COPD later in life.

OCCUPATIONAL EXPOSURES

Increased respiratory symptoms and airflow obstruction have been suggested to result from exposure to dust and fumes. Several specific occupational exposures, including coal mining, gold mining, and cotton textile dust, have been implicated as risk factors for chronic airflow obstruction. Although nonsmokers in these occupations can develop some reductions in FEV₁, the importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain for most of these exposures. However, among coal miners, coal mine dust exposure was a significant risk factor for emphysema in both smokers and nonsmokers. In most cases, the magnitude of these occupational exposures on COPD risk is likely substantially less important than the effect of cigarette smoking.

AMBIENT AIR POLLUTION

Some investigators have reported increased respiratory symptoms in those living in urban compared to rural areas, which may relate to increased pollution in the urban settings. However, the relationship of air pollution to chronic airflow obstruction remains unproved. Prolonged exposure to smoke produced by biomass combustion—a common mode of cooking in some countries—also appears to be a significant risk factor for COPD, particularly among women.

PASSIVE, OR SECOND-HAND, SMOKING EXPOSURE

Exposure of children to maternal smoking results in significantly reduced lung growth. In utero, tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions often observed in COPD remains uncertain.

GENETIC CONSIDERATIONS

 Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe I^{AT} deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.

Antitrypsin Deficiency Many variants of the protease inhibitor (PI or *SERPINA1*) locus that encodes I^{AT} have been described. The common M allele is associated with normal I^{AT} levels. The S allele, associated with slightly reduced I^{AT} levels, and the Z allele, associated with markedly reduced I^{AT} levels, also occur with frequencies of >1% in most white populations. Rare individuals inherit null alleles, which lead to the absence of any I^{AT} production through

a heterogeneous collection of mutations. Individuals with two Z alleles or one Z and one null allele are referred to as Pi^{Z} , which is the most common form of severe I^{AT} deficiency.

Although only ~1% of COPD patients are found to have severe I^{AT} deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD. Pi^{Z} individuals often develop early-onset COPD, but the ascertainment bias in the published series of Pi^{Z} individuals—which have usually included many Pi^{Z} subjects who were tested for

I^{AT} deficiency because they had COPD—means that the fraction of Pi^{Z} individuals who will develop COPD and the age-of-onset distribution for the development of COPD in Pi^{Z} subjects remain unknown. Approximately 1 in 3000 individuals in the United States inherits severe I^{AT} deficiency, but only a small minority of these individuals has been identified. The clinical laboratory test used most frequently to screen for I^{AT} deficiency is measurement of the immunologic level of I^{AT} in serum (see “Laboratory Findings”).

A significant percentage of the variability in pulmonary function among Pi^{Z} individuals is explained by cigarette smoking; cigarette smokers with severe I^{AT} deficiency are more likely to develop COPD at early ages. However, the development of COPD in Pi^{Z} subjects, even among current or ex-smokers, is not absolute. Among Pi^{Z} nonsmokers, impressive variability has been noted in the development of airflow obstruction. Asthma and male gender also appear to increase the risk of COPD in Pi^{Z} subjects. Other genetic and/or environmental factors likely contribute to this variability.

Specific treatment in the form of I^{AT} augmentation therapy is available for severe I^{AT} deficiency as a weekly IV infusion (see “Treatment,” below).

The risk of lung disease in heterozygous Pi^{MZ} individuals, who have intermediate serum levels of I^{AT} (~60% of Pi^{MM} levels), has been controversial. Several recent studies have demonstrated that Pi^{MZ} subjects who smoke are likely at increased risk for the development of COPD. However, I^{AT} augmentation therapy is not recommended for use in Pi^{MZ} subjects.

Other Genetic Risk Factors Studies of pulmonary function measurements performed in general population samples have indicated that genetic factors other than PI type influence variation in pulmonary function. Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated.

GWAS have identified >80 regions of the genome that contain COPD susceptibility loci, including a region near the *HHIP* gene on chromosome 4, a cluster of genes on chromosome 15 (including components of the nicotinic acetylcholine receptor and another gene, *IREB2*, related to mitochondrial iron regulation), and a region within a gene of unknown function (*FAM13A*). As with most other complex diseases, the risk associated with individual GWAS loci is modest, but these genetic determinants may identify important biological pathways related to COPD. Gene-targeted murine models for *HHIP*, *FAM13A*, and *IREB2* exposed to chronic cigarette smoke had altered emphysema susceptibility, suggesting that those genes are likely to be involved in COPD pathogenesis.

NATURAL HISTORY

The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smoking exposure during growth and development, and the baseline lung function of the individual; other environmental factors may have similar effects. Most individuals follow a steady trajectory of increasing pulmonary function with growth during childhood and adolescence, followed by a plateau in early adulthood, and then gradual decline with aging. Individuals appear to track in their quantile of pulmonary function based on environmental and genetic factors that put them on different tracks. The risk of eventual mortality from COPD is closely associated with reduced levels of FEV₁. A graphic depiction of the natural history of COPD is shown as a function of the influences on tracking curves of FEV₁ in Fig. 292-4. Death or disability from COPD can result from a normal rate of decline after a reduced growth

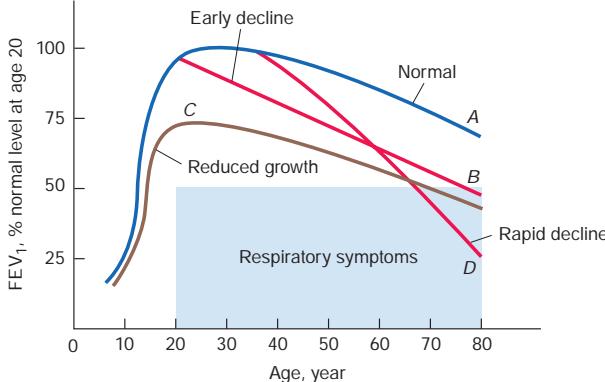


FIGURE 292-4 Hypothetical tracking curves of forced expiratory volume in 1 s (FEV₁) for individuals throughout their life spans. The normal pattern of growth and decline with age is shown by curve A. Significantly reduced FEV₁ (<65% of predicted value at age 20) can develop from a normal rate of decline after a reduced pulmonary function growth phase (curve C), early initiation of pulmonary function decline after normal growth (curve B), or accelerated decline after normal growth (curve D). (From B Rijcken: Doctoral dissertation, p 133, University of Groningen, 1991; with permission.)

phase (curve C), an early initiation of pulmonary function decline after normal growth (curve B), or an accelerated decline after normal growth (curve D). Although accelerated rates of lung function decline have classically been associated with COPD, recent analyses of several population-based cohorts demonstrated that many subjects meeting the spirometric criteria for COPD had reduced growth but normal rates of lung function decline. The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking), with smoking cessation at an earlier age providing a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed. The absolute annual loss in FEV₁ tends to be highest in mild COPD and lowest in very severe COPD. Multiple genetic factors influence the level of pulmonary function achieved during growth.

In chronic smokers, substantial chest CT changes (emphysema and airway wall thickening) have been identified in subjects with normal physiology (normal FEV₁ and FEV₁/FVC). COPD in these subjects commonly progresses in two primary patterns. Subjects with an emphysema-predominant pattern show emphysema early and classically progress through GOLD 1 to GOLD 2–4. Subjects with an airway disease-predominant pattern typically show initial evidence of airway inflammation and progress with little emphysema early as FEV₁ falls while retaining a normal FEV₁/FVC ratio. This is termed *preserved ratio-impaired spirometry* (PRI Sm) physiology. These subjects tend to develop emphysema late and can progress directly to GOLD 3 and 4 with severe, end-stage COPD.

CLINICAL PRESENTATION

HISTORY

The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea. Many patients have such symptoms for months or years before seeking medical attention. Although the development of airflow obstruction is a gradual process, many patients date the onset of their disease to an acute illness or exacerbation. A careful history, however, usually reveals the presence of respiratory symptoms prior to the acute exacerbation. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious. It is best elicited by a careful history focused on typical physical activities and how the patient's ability to perform them has changed. Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for many patients with COPD. Conversely, activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated. Examples of such activities include

pushing a shopping cart or walking on a treadmill. As COPD advances, the principal feature is worsening dyspnea on exertion with increasing intrusion on the ability to perform vocational or avocational activities. In the most advanced stages, patients are breathless doing basic activities of daily living.

Accompanying worsening airflow obstruction is an increased frequency of exacerbations (described below). Patients may also develop resting hypoxemia and require institution of supplemental oxygen.

PHYSICAL FINDINGS

In the early stages of COPD, patients usually have an entirely normal physical examination. Current smokers may have signs of active smoking, including an odor of smoke or nicotine staining of fingernails. In patients with more severe disease, the physical examination of the lungs is notable for a prolonged expiratory phase and may include expiratory wheezing. In addition, signs of hyperinflation include a barrel chest and enlarged lung volumes with poor diaphragmatic excursion as assessed by percussion. Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration, sitting in the characteristic "tripod" position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles. Patients may develop cyanosis, visible in the lips and nail beds.

Traditional teaching is that patients with predominant emphysema, termed "pink puffers," are thin, noncyanotic at rest, and have prominent use of accessory muscles, and patients with chronic bronchitis are more likely to be heavy and cyanotic ("blue bloaters"). However, current evidence demonstrates that most patients have elements of both chronic bronchitis and emphysema and that the physical examination does not reliably differentiate the two entities.

Advanced disease may be accompanied by cachexia, with significant weight loss and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF- α). Such wasting is an independent poor prognostic factor in COPD. Some patients with advanced disease have paradoxical inward movement of the rib cage with inspiration (Hoover's sign), the result of alteration of the vector of diaphragmatic contraction on the rib cage due to chronic hyperinflation.

Signs of overt right heart failure, termed *cor pulmonale*, are relatively infrequent since the advent of supplemental oxygen therapy.

Clubbing of the digits is not a sign of COPD, and its presence should alert the clinician to initiate an investigation for causes of clubbing. In COPD patients, the development of lung cancer is the most likely explanation for newly developed clubbing.

LABORATORY FINDINGS

The hallmark of COPD is airflow obstruction (discussed above). Pulmonary function testing shows airflow obstruction with a reduction in FEV₁ and FEV₁/FVC (Chap. 285). With worsening disease severity, lung volumes may increase, resulting in an increase in total lung capacity, functional residual capacity, and residual volume. In patients with emphysema, the diffusing capacity may be reduced, reflecting the lung parenchymal destruction characteristic of the disease. The degree of airflow obstruction is an important prognostic factor in COPD and is the basis for the GOLD spirometric severity classification (Table 292-1). Although the degree of airflow obstruction generally correlates with the presence and severity of respiratory symptoms, exacerbations, emphysema, and hypoxemia, the correlations are far from perfect. Thus, clinical features should be carefully assessed in each individual patient with COPD to determine the most appropriate therapies. It has been shown that a multifactorial index (BODE), incorporating airflow obstruction, exercise performance, dyspnea, and body mass index, is a better predictor of mortality. Recently, GOLD added additional elements to their COPD classification system incorporating respiratory symptoms and exacerbation history; these metrics are used to guide COPD treatment (see below).

Arterial blood gases and oximetry may demonstrate resting or exertional hypoxemia. Arterial blood gases provide additional information about alveolar ventilation and acid-base status by measuring arterial

2186 PCO_2 and pH. The change in pH with PCO_2 is 0.08 units/10 mmHg acutely and 0.03 units/10 mmHg in the chronic state. Knowledge of the arterial pH therefore allows the classification of ventilatory failure, defined as $\text{PCO}_2 > 45 \text{ mmHg}$, into acute or chronic conditions with acute respiratory failure being associated with acidemia. The arterial blood gas is an important component of the evaluation of patients presenting with symptoms of an exacerbation. An elevated hematocrit suggests the presence of chronic hypoxemia, as does the presence of signs of right ventricular hypertrophy.

Radiographic studies may assist in the classification of the type of COPD. Increased lung volumes and flattening of the diaphragm suggest hyperinflation but do not provide information about chronicity of the changes. Obvious bullae, paucity of parenchymal markings, or hyperlucency on chest x-ray suggests the presence of emphysema. Chest CT scan is the current definitive test for establishing the presence or absence of emphysema, the pattern of emphysema, and the presence of significant disease involving medium and large airways (Fig. 292-2). It also enables the discovery of coexisting interstitial lung disease and bronchiectasis. Smokers with COPD are at high risk for development of lung cancer, which can be identified on a chest CT scan. In advanced COPD, CT scans can help determine the possible value of surgical therapy (described below).

Recent guidelines have suggested testing for $\alpha_1\text{-AT}$ deficiency in all subjects with COPD or asthma with chronic airflow obstruction. Measurement of the serum $\alpha_1\text{-AT}$ level is a reasonable initial test. For subjects with low $\alpha_1\text{-AT}$ levels, the definitive diagnosis of $\alpha_1\text{-AT}$ deficiency requires PI type determination. This is typically performed by isoelectric focusing of serum or plasma, which reflects the genotype at the PI locus for the common alleles and many of the rare PI alleles as well. Molecular genotyping can be performed for the common PI alleles (M, S, and Z), and DNA sequencing can detect other rare deficiency variants.

TREATMENT

Chronic Obstructive Pulmonary Disease

STABLE PHASE COPD

The two main goals of therapy are to provide symptomatic relief (reduce respiratory symptoms, improve exercise tolerance, and improve health status) and reduce future risk (prevent disease progression, prevent and treat exacerbations, and reduce mortality). The institution of therapies should be based on symptom assessment, benefits of therapy, potential risks, and costs. **Figure 292-5** provides the currently suggested categories of COPD patients based on respiratory symptoms and risk for exacerbations. Response to therapy should be assessed, and decisions should be made whether or not to continue or alter treatment.

Three interventions—smoking cessation, oxygen therapy in chronically hypoxic patients, and lung volume reduction surgery (LVRS) in selected patients with emphysema—have been demonstrated to improve survival of patients with COPD. Recent studies indicate that triple inhaled therapy (long-acting beta agonist bronchodilator, long-acting muscarinic antagonist bronchodilator and inhaled corticosteroid) reduces mortality in selected patients with COPD. There is a suggestion that inhaled LAMA bronchodilators may reduce mortality.

PHARMACOTHERAPY

Smoking Cessation (See also Chap. 454) It has been shown that middle-aged smokers who were able to successfully stop smoking experienced a significant improvement in the rate of decline in pulmonary function, often returning to annual changes similar to that of nonsmoking patients. In addition, smoking cessation improves survival. Thus, all patients with COPD should be strongly urged to quit smoking and educated about the benefits of quitting. An emerging body of evidence demonstrates that combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation. There are

Exacerbation History		COPD Severity Group	
2 or 1 with hospital admission	C Low symptoms, High risk	D High symptoms, High risk	
0 or 1 (without hospital admission)	A Low symptoms, Low risk	B High symptoms, Low risk	
	mMRC 0–1 or CAT <10	mMRC 2 or CAT ≥10	
			Symptoms

FIGURE 292-5 Chronic obstructive pulmonary disease (COPD) severity assessment. COPD severity categories are based on respiratory symptoms (based on the Modified Medical Research Council Dyspnea Scale [mMRC] or COPD Assessment Test [CAT]) and annual frequency of COPD exacerbations. The mMRC provides a single number for degree of breathlessness: 0—only with strenuous activity; 1—hurrying on level ground or walking up a slight hill; 2—walk slower than peers or stop walking at their own pace; 3—walking about 100 yards or after a few minutes on level ground; 4—too breathless to leave the house or when dressing. The CAT is an eight-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea on one flight of stairs, limitation in home activities, confidence in leaving the home, sleep, and energy. Range of total score is 0–40. Both mMRC and CAT are available from Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. (Reproduced with permission from Global Strategy for Diagnosis, Management and Prevention of COPD 2017, ©.)

three principal pharmacologic approaches to the problem: nicotine replacement therapy available as gum, transdermal patch, lozenge, inhaler, and nasal spray; bupropion; and varenicline, a nicotinic acid receptor agonist/antagonist. Current recommendations from the U.S. Surgeon General are that all adult, nonpregnant smokers considering quitting be offered pharmacotherapy, in the absence of any contraindication to treatment. Smoking cessation counseling is also recommended and free counseling is available through state Smoking QuitLines.

Bronchodilators In general, bronchodilators are the primary treatment for almost all patients with COPD and are used for symptomatic benefit and to reduce exacerbations. The inhaled route is preferred for medication delivery, because side effects are less than with systemic medication delivery. In symptomatic patients, both regularly scheduled use of long-acting agents and as-needed short-acting medications are indicated. **Figure 292-6** provides suggestions for prescribing inhaled medication therapy based on grouping patients by severity of symptoms and risk of exacerbations.

Muscarinic Antagonists Short-acting ipratropium bromide improves symptoms with acute improvement in FEV₁. Long-acting muscarinic antagonists (LAMAs, including aclidinium, glycopyrrate, glycopyrronium, retevabacin, tiotropium, and umeclidinium) improve symptoms and reduce exacerbations. In a large randomized clinical trial, there was a trend toward reduced mortality rate in tiotropium-treated patients that approached statistical significance. Side effects are minor; dry mouth is the most frequent side effect.

Beta Agonists Short-acting beta agonists ease symptoms with acute improvements in lung function. Long-acting beta agonists (LABAs) provide symptomatic benefit and reduce exacerbations, though to a lesser extent than an LAMA. Currently available long-acting inhaled beta agonists are arformoterol, formoterol, indacaterol, olodaterol, salmeterol, and vilanterol. The main side effects are tremor and tachycardia.

Combinations of Beta Agonist–Muscarinic Antagonist The combination inhaled long-acting beta agonist and muscarinic antagonist therapy has been demonstrated to provide improvement in

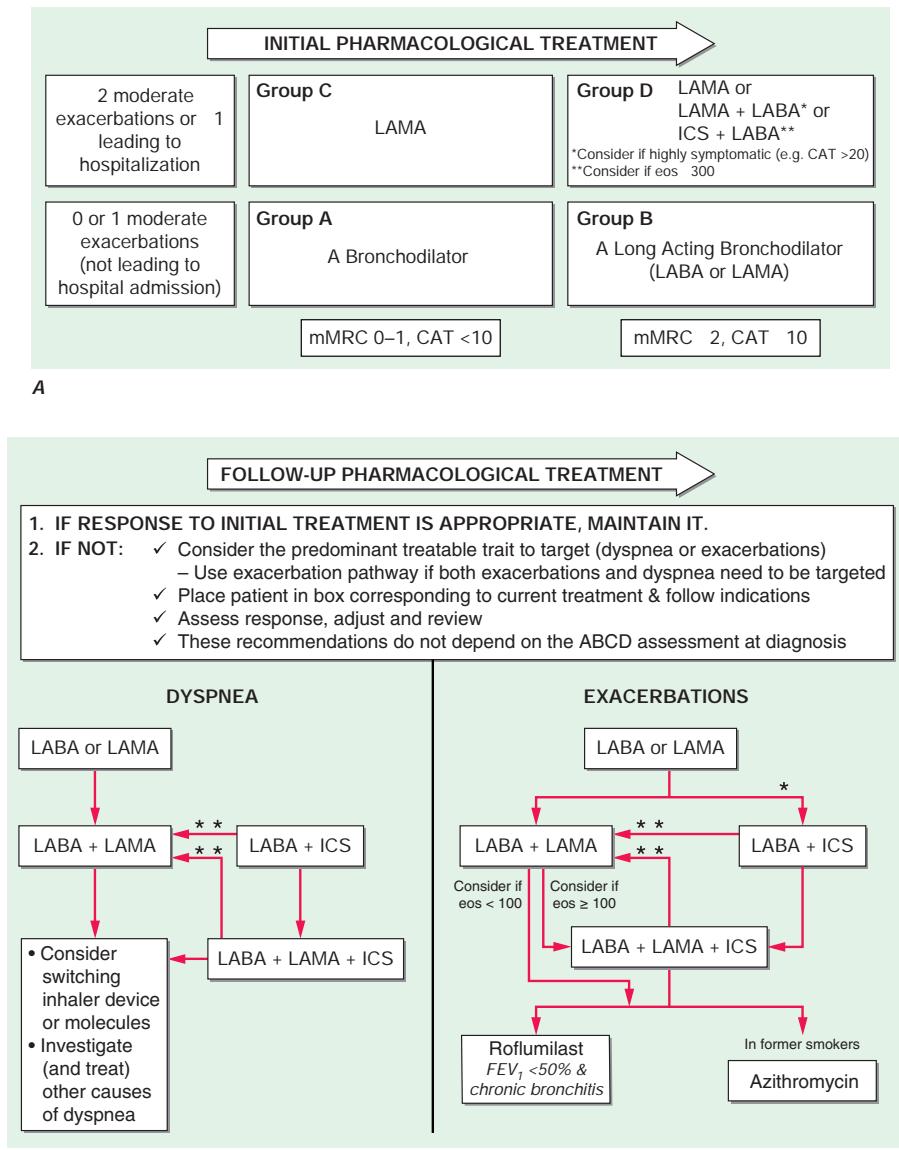


FIGURE 292-6 Medication therapy for stable chronic obstructive pulmonary disease (COPD). Initial pharmacological therapy (Panel A) is based on both COPD exacerbations and respiratory symptoms (assessed through the modified Medical Research Council (mMRC) dyspnea questionnaire or the COPD Assessment Test (CAT)). Follow-up pharmacological therapy (Panel B) is based on response to treatment initiation and reassessment of symptoms and exacerbations. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2021. *For Panel B: consider if eos 300 or eos ≥ 100 AND 2 moderate exacerbations/1 hospitalization. **Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS. CAT™, COPD Assessment Test™; Eos, blood eosinophil count in cells per microliter; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea questionnaire. (Reproduced with permission from the Global Strategy for Diagnosis, Management and Prevention of COPD 2021, ©.)

lung function that is greater than either agent alone and reduces exacerbations.

Inhaled Corticosteroids The main role of ICS is to reduce exacerbations. In population studies, patients with an eosinophil count of <100 cells per microliter do not benefit, while benefit increases as eosinophil counts rise above 100. ICS are never used alone in COPD due to little symptomatic benefit but, rather, are combined with a LABA or used with a LABA and LAMA. Their use has been associated with increased rates of oropharyngeal candidiasis and pneumonia and in some studies an increased rate of loss of bone density and development of cataracts. A trial of ICS should be

considered in patients with frequent exacerbations, defined as two or more per year or in patients hospitalized with one exacerbation. In stable patients without exacerbations, ICS withdrawal may be considered. Patients who continue to smoke cigarettes do not benefit as greatly from ICS use. Although ICS withdrawal does not lead to an increase in exacerbations, there may be a small decline in lung function.

Oral Glucocorticoids The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio. The chronic use of oral glucocorticoids is associated with significant side effects, including osteoporosis, weight

gain, cataracts, glucose intolerance, and increased risk of infection. A study demonstrated that patients tapered off chronic low-dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function.

Theophylline Theophylline produces modest improvements in airflow and vital capacity, but is not first-line therapy due to side effects and drug interactions. Nausea is a common side effect; tachycardia and tremor have also been reported. Monitoring of blood theophylline levels is required to minimize toxicity.

PDE4 Inhibitors The selective phosphodiesterase 4 (PDE4) inhibitor roflumilast has been demonstrated to reduce exacerbation frequency in patients with severe COPD, chronic bronchitis, and a prior history of exacerbations; its effects on airflow obstruction and symptoms are modest, and side effects (including nausea, diarrhea, and weight loss) are common.

Antibiotics There are strong data implicating bacterial infection as a precipitant of a substantial portion of exacerbations. A randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antimicrobial properties, administered daily to subjects with a history of exacerbation in the past 6 months demonstrated a reduced exacerbation frequency and longer time to first exacerbation in the macrolide-treated cohort (hazard ratio, 0.73). Azithromycin was most effective in older patients and milder GOLD stages; there was little benefit in current smokers.

Oxygen Supplemental O₂ is the only pharmacologic therapy demonstrated to unequivocally decrease mortality in patients with COPD. For patients with resting hypoxemia (resting O₂ saturation 88% in any patient or 89% with signs of pulmonary arterial hypertension, right heart failure or erythrocytosis), the use of O₂ has been demonstrated to have a significant impact on mortality. Patients meeting these criteria should be on continuous oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen is used. Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.

A recent study failed to demonstrate mortality benefits to COPD patients with moderate hypoxemia at rest or with hypoxemia only with activity.

AT Augmentation Therapy Specific treatment in the form of IV AT augmentation therapy is available for individuals with severe AT deficiency. Despite sterilization procedures for these blood-derived products and the absence of reported cases of viral infection from therapy, some physicians recommend hepatitis B vaccination prior to starting augmentation therapy. Although biochemical efficacy of AT augmentation therapy has been shown, the benefits of AT augmentation therapy are controversial. A randomized study suggested a reduction in emphysema progression in patients receiving AT augmentation therapy. Eligibility for AT augmentation therapy requires a serum AT level <11 μM (~50 mg/dL). Typically, Pi^z individuals will qualify, although other rare types associated with severe deficiency (e.g., null-null) are also eligible. Because only a fraction of individuals with severe AT deficiency will develop COPD, AT augmentation therapy is not recommended for severely AT-deficient persons with normal pulmonary function and a normal chest CT scan.

NONPHARMACOLOGIC THERAPIES

Patients with COPD should receive the influenza vaccine annually. Pneumococcal vaccines and vaccination for *Bordetella pertussis* are recommended.

Pulmonary Rehabilitation This refers to a comprehensive treatment program that incorporates exercise, education, and psychosocial and nutritional counseling. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6- to 12-month period.

Lung Volume Reduction Surgery In carefully selected patients with emphysema, surgery to remove the most emphysematous portions of lung improves exercise capacity, lung function, and survival. The anatomic distribution of emphysema and postrehabilitation exercise capacity are important prognostic characteristics. Patients with upper lobe-predominant emphysema and a low postrehabilitation exercise capacity are most likely to benefit from LVRS.

Patients with an FEV₁ <20% of predicted and either diffusely distributed emphysema on CT scan or diffusing capacity of lung for carbon monoxide (DL_{CO}) <20% of predicted have increased mortality after the procedure, and thus are not candidates for LVRS.

Methods of achieving lung volume reduction by using bronchoscopic techniques have recently been approved by the U.S. Food and Drug Administration; they appear to be beneficial in selected emphysema patients.

Lung Transplantation (See also Chap. 298) COPD is currently the second leading indication for lung transplantation. Current recommendations are that candidates for lung transplantation should have very severe airflow obstruction, severe disability despite maximal medical therapy, and be free of significant comorbid conditions such as liver, renal, or cardiac disease.

EXACERBATIONS OF COPD

Exacerbations are a prominent feature of the natural history of COPD. Exacerbations are episodic acute worsening of respiratory symptoms, including increased dyspnea, cough, wheezing, and/or change in the amount and character of sputum. They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat. The strongest single predictor of exacerbations is a history of a previous exacerbation. The frequency of exacerbations increases as airflow obstruction worsens; patients with severe (FEV₁ <50% predicted) or very severe airflow obstruction (FEV₁ <30% predicted) on average have 1–3 episodes per year. However, some individuals with very severe airflow obstruction do not have frequent exacerbations. Other factors, such as an elevated ratio of the diameter of the pulmonary artery to aorta on chest CT and gastroesophageal reflux, are also associated with increased risk of COPD exacerbations. Economic analyses have shown that >70% of COPD-related health care expenditures are due to emergency department visits and hospital care for COPD exacerbations; this translates to over \$10 billion annually in the United States.

Precipitating Causes and Strategies to Reduce Frequency of Exacerbations A variety of stimuli may result in the final common pathway of airway inflammation and increased respiratory symptoms that are characteristic of COPD exacerbations. Studies suggest that acquiring a new strain of bacteria is associated with increased near-term risk of exacerbation and that bacterial infection/superinfection is involved in >50% of exacerbations. Viral respiratory infections are present in approximately one-third of COPD exacerbations. In a significant minority of instances (20–35%), no specific precipitant can be identified.

Patient Assessment An attempt should be made to establish the severity of the exacerbation as well as the severity of preexisting COPD. The more severe either of these two components, the more likely that the patient will require hospital admission. The history should include quantification of the degree and change in dyspnea by asking about breathlessness during activities of daily living and typical activities for the patient. The patient should be asked about fever; change in character of sputum; and associated symptoms such as wheezing, nausea, vomiting, diarrhea, myalgias, and chills. Inquiring about the frequency and severity of prior exacerbations can provide important information; the single greatest risk factor for hospitalization with an exacerbation is a history of previous hospitalization.

The physical examination should incorporate an assessment of the degree of distress of the patient. Specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete

sentences, and the patient's mental status. The chest examination should establish the presence or absence of focal findings, degree of air movement, presence or absence of wheezing, asymmetry in the chest examination (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and the presence or absence of paradoxical motion of the abdominal wall.

Patients with severe underlying COPD, who are in moderate or severe distress, or those with focal findings should have a chest x-ray or chest CT scan. Approximately 25% of x-rays in this clinical situation will be abnormal, with the most frequent findings being pneumonia and congestive heart failure. Patients with advanced COPD, a history of hypercarbia, or mental status changes (confusion, sleepiness) or those in significant distress should have an arterial blood gas measurement. The presence of hypercarbia, defined as a $\text{PCO}_2 >45 \text{ mmHg}$, has important implications for treatment (discussed below). In contrast to its utility in the management of exacerbations of asthma, measurement of pulmonary function has not been demonstrated to be helpful in the diagnosis or management of exacerbations of COPD. Pulmonary embolus (PE) should also be considered, as the incidence of PE is increased in COPD exacerbations.

The need for inpatient treatment of exacerbations is suggested by the presence of respiratory acidosis and hypercarbia, new or worsening hypoxemia, severe underlying disease, and those whose living situation is not conducive to careful observation and the delivery of prescribed treatment.

TREATMENT OF ACUTE EXACERBATIONS

Bronchodilators Typically, patients are treated with inhaled beta agonists and muscarinic antagonists. These may be administered separately or together, and the frequency of administration depends on the severity of the exacerbation. Patients are often treated initially with nebulized therapy, as such treatment is often easier to administer in those in respiratory distress. It has been shown, however, that conversion to metered-dose inhalers is effective when accompanied by education and training of patients and staff. This approach has significant economic benefits and also allows an easier transition to outpatient care. The addition of methylxanthines (theophylline) to this regimen can be considered, although convincing proof of its efficacy is lacking. If methylxanthines are added, serum levels should be monitored in an attempt to minimize toxicity.

Antibiotics Patients with COPD are frequently colonized with potential respiratory pathogens, and it is often difficult to identify conclusively a specific species of bacteria responsible for a particular clinical event. Bacteria frequently implicated in COPD exacerbations include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Chlamydia pneumoniae*; viral pathogens are also common etiologies of exacerbations. The choice of antibiotic should be based on local patterns of antibiotic susceptibility of the above bacterial pathogens as well as the patient's clinical condition. Patients with moderate or severe exacerbations are usually treated with antibiotics, even in the absence of data implicating a specific pathogen.

In patients admitted to the hospital, the use of systemic glucocorticoids reduces the length of stay, hastens recovery, and reduces the chance of subsequent exacerbation or relapse. One study demonstrated that 2 weeks of glucocorticoid therapy produced benefit indistinguishable from 8 weeks of therapy. Current recommendations suggest 30–40 mg of oral prednisolone or its equivalent typically for a period of 5–10 days in outpatients. Hyperglycemia, particularly in patients with preexisting diagnosis of diabetes, is the most frequently reported acute complication of glucocorticoid treatment.

Oxygen Supplemental O_2 should be supplied to maintain oxygen saturation $>90\%$. Studies have demonstrated that in patients with both acute and chronic hypercarbia, the administration of supplemental O_2 does not reduce minute ventilation. It does, in some patients, result in modest increases in arterial PCO_2 , chiefly by altering ventilation-perfusion relationships within the lung. This

should not deter practitioners from providing the oxygen needed to correct hypoxemia.

Mechanical Ventilatory Support The initiation of noninvasive positive-pressure ventilation (NIPPV) in patients with respiratory failure, defined as $\text{Paco}_2 >45 \text{ mmHg}$, results in a significant reduction in mortality rate, need for intubation, complications of therapy, and hospital length of stay. Contraindications to NIPPV include cardiovascular instability, impaired mental status, inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or significant burns.

Invasive (conventional) mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life-threatening hypoxemia, severe hypercarbia and/or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications. The goal of mechanical ventilation is to correct the aforementioned conditions. Factors to consider during mechanical ventilatory support include the need to provide sufficient expiratory time in patients with severe airflow obstruction and the presence of auto-PEEP (positive end-expiratory pressure), which can result in patients having to generate significant respiratory effort to trigger a breath during a demand mode of ventilation. The mortality rate of patients requiring mechanical ventilatory support is 17–30% for that particular hospitalization. For patients aged >65 admitted to the intensive care unit for treatment, the mortality rate doubles over the next year to 60%, regardless of whether mechanical ventilation was required.

Following a hospitalization for COPD, about 20% of patients are rehospitalized in the subsequent 30 days and 45% are hospitalized in the next year. Mortality following hospital discharge is about 20% in the following year.

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Diffuse parenchymal lung diseases include a large number (>200) of heterogeneous conditions that affect the lung parenchyma with varying degrees of inflammation and fibrosis. While remodeling of the interstitial space, the region between the epithelium and endothelium, tends to be the dominant site of involvement for most of the interstitial lung diseases (ILDs), it is important to recognize the prominent role of the alveolar epithelium and endothelial cells (including both airways and vessels) in the pathogenesis of these ILDs.

Despite the diverse array of conditions, most patients ultimately diagnosed with an ILD will come to medical attention with reports of progressive exertional dyspnea or a persistent dry cough. However, because some ILDs are part of multisystem disorders, some patients will be identified based on nonrespiratory symptomatology (e.g., skin thickening in the setting of systemic sclerosis, [Chap. 359](#)) or physical examination findings (e.g., ulnar deviation of the fingers in the setting of rheumatoid arthritis [RA], [Chap. 358](#)). Additionally, ILDs can also be identified incidentally based on the results of abnormal pulmonary function tests, chest x-rays (CXR), computed tomography (CT) studies of both the chest and abdomen (which can both visualize, at least a portion, of the lung parenchyma), and positron emission tomography (PET) scans. It is important to remember that ILDs can be associated with high rates of morbidity and mortality, and although prognosis depends on both disease extent and specificity, this fact makes these important disorders to recognize in a timely manner.

Owing to a variety of clinical presentations, as well as overlapping imaging and histopathologic findings ([Table 293-1](#)), ILDs can be difficult to diagnose. A generally accepted central tenet of ILD diagnosis is that the combined weight of clinical data, laboratory studies,

pulmonary function testing, imaging findings, and histopathology (if obtained) are jointly required to make a confident diagnosis. No single piece of data confers a diagnosis alone. For example, a lung biopsy demonstrating a usual interstitial pneumonia (UIP) pattern is helpful in diagnosing a patient with idiopathic pulmonary fibrosis (IPF) but can also be present in some connective tissue diseases (CTDs) (e.g., RA-associated ILD, [Chap. 358](#)). In light of this challenge, most ILD centers recommend a multidisciplinary approach to the diagnosis (and in some cases the management) of ILDs. An example of a multidisciplinary approach might include a conference attended by pulmonologists, rheumatologists, radiologists, and pathologists where all of the data generated on a patient can be discussed and reviewed jointly by those with unique sets of expertise in the care of patients with ILD.

While there are numerous ways to categorize the ILDs, one classic approach is to divide the ILDs into those of known and unknown causes ([Fig. 293-1](#)). Although even this approach has limitations (e.g., genetic studies demonstrate that a significant portion of familial pulmonary fibrosis and IPF [classically described as diseases of unknown cause] may be explained, in part, by genetic factors), it is a useful place to start. Known causes of ILD include occupational exposures (e.g., asbestos), medications (e.g., nitrofurantoin), and those related to an underlying systemic disease (e.g., cryptogenic organizing pneumonia [COP] in the setting of polymyositis). Unknown causes of ILD include groups of rare disorders often with classic presentations (e.g., a spontaneous pneumothorax in a young female with diffuse cystic changes on a chest CT might suggest lymphangioleiomyomatosis [LAM]) and the most common group of ILDs, the idiopathic interstitial pneumonias (IIPs). Granulomatous lung diseases straddle both known (e.g., hypersensitivity pneumonitis [HP] due to chronic bird exposure, [Chap. 288](#)) and unknown (e.g., sarcoidosis, [Chap. 367](#)) causes and are often separated due to their unique presentations, imaging findings, and diagnostic evaluation. Equally important to knowledge of disease classification is knowledge of disease prevalence. Although there is variability within different demographic groups, most studies demonstrate that IPF, the

TABLE 293-1 Common Interstitial Lung Disease (ILD) Findings

	IPF	NONSPECIFIC INTERSTITIAL PNEUMONIA	RESPIRATORY BRONCHIOLITIS ASSOCIATED ILD	SYSTEMIC SCLEROSIS ASSOCIATED ILD	SARCOIDOSIS
Clinical symptoms	Gradual onset of SOB, dry cough. Unusual in older adults.	Subacute onset of SOB, dry cough. Frequently associated with other conditions.	Can be asymptomatic, or have SOB and cough.	Gradual onset of SOB, dry cough. Fatigue, tightening of skin, exaggerated cold response, reflux, and difficulty swallowing.	Can be asymptomatic, or have SOB and cough. Can also have fatigue, palpitations, eye, skin, and joint findings.
Physical exam findings	Frequent rales at lung bases; digital clubbing is common.	Frequent rales. Clubbing is less common.	Rales common. Clubbing is rare.	Can have rales in isolation. Also skin thickening, joint swelling, and telangiectasias.	Can be normal; rales may be present. Can have skin findings, joint pain, and enlarged lymph nodes.
Exposures	Idiopathic but many exposed to smoke. Genetic findings may explain more than one-third of the risk of the disease.	Can be idiopathic but should prompt consideration for associated conditions.	Strong association with smoking.	Mostly unknown; some debate about solvent and silicate exposures.	Mostly unknown, although silicate dusts thought to play a role in some cases.
HRCT findings	Bilateral subpleural reticular changes most prominent in lower, posterior lung zones. Traction bronchiectasis and honeycombing common. Classic usual interstitial pneumonia (UIP) pattern is considered diagnostic.	Peripheral subpleural ground glass and reticular patterns. Traction bronchiectasis is common, but honeycombing is rare. HRCT not diagnostic.	Diffuse patchy centrilobular ground glass nodules.	Can have UIP or nonspecific interstitial pneumonia (NSIP) patterns, also dilated esophagus, occasional mediastinal calcifications, and pulmonary vascular enlargement.	Can have mediastinal and hilar lymphadenopathy. Peribronchovascular reticular-nodular findings.
Histopathology	UIP pattern including fibroblastic foci, temporal and spatial heterogeneity, honeycombing.	Cellular or fibrotic pattern of NSIP. More uniform than a UIP pattern.	Respiratory bronchiolitis with adjacent inflammatory and fibrosing changes. Pigment-laden macrophages.	Both UIP or NSIP patterns can occur.	Noncaseating granulomas.
Clinical course	50% 3- to 5-year mortality.	18% 5-year mortality.	25% 7-year mortality.	20–30% 10-year mortality.	Generally low but varies by state.

Abbreviations: HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SOB, shortness of breath.

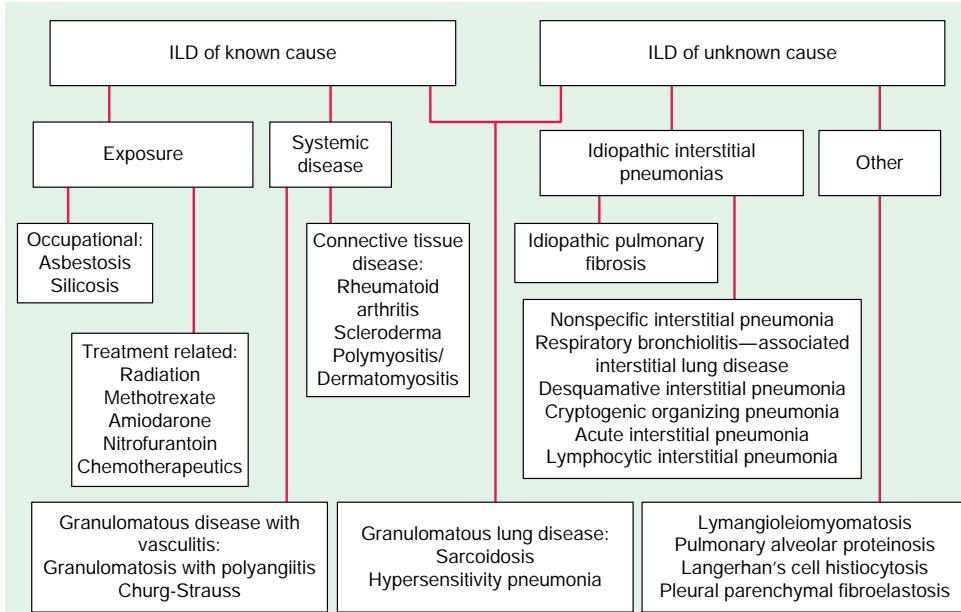


FIGURE 293-1 Classification of interstitial lung disease. This algorithm represents a common approach to subclassifying the interstitial lung diseases. It is typical to divide the interstitial lung diseases into those of known and unknown causes (although it is important to note that genetic studies demonstrate that a significant portion of familial and idiopathic pulmonary fibrosis [classically described as diseases of unknown cause] may be explained, in part, by genetic factors). The idiopathic interstitial pneumonias were more precisely defined by a 2002 study as described in Am J Respir Crit Care Med 165:277, 2002, referenced in the Further Reading list.

sarcoidosis ([Chap. 367](#)), and ILDs related to CTDs ([Chap. 413](#)) as a group are among the most common forms of ILD.

DIAGNOSTIC APPROACH

The initial diagnostic approach to diffuse parenchymal lung disease is often broader than a focus on ILD and should include an evaluation for alternate causes including cardiovascular disease (e.g., heart failure, [Chap. 258](#)), diffuse infections (e.g., *pneumocystis* pneumonia, [Chap. 220](#)), and malignancy (e.g., bronchoalveolar cell carcinoma, [Chap. 315 in HPIM 19e](#)). This chapter will focus on the diagnostic evaluation that helps to distinguish among the various forms of ILD.

HISTORY

Age Age at presentation has a strong influence on the pretest probability that IPF, in particular, is present. For example, IPF occurs most commonly in patients aged >60 and is quite rare among patients aged <50. In fact, in patients aged >65 without strong evidence for an alternate diagnosis, atypical chest CT findings are still more likely to result in a histopathologic diagnosis of UIP (a pathologic hallmark of IPF) than they are to result in an alternate IIP diagnosis. Other common ILDs, such as sarcoidosis and CTD-associated ILD, and less common ILDs, such as LAM and pulmonary Langerhans cell histiocytosis (PLCH), tend to present between the ages of 20 and 40.

Sex Although less influential than age, sex has some influence on likelihood of various ILDs. LAM (and the related disorder tuberous sclerosis) ([see Chap. 315 in HPIM 19e](#)) is a disorder that is frequently diagnosed in young women. Many CTD-associated ILDs are more common among women, with the exception of RA-associated ILD, which is more common among men. IPF and occupational/exposure-related ILDs (likely due to work-related exposures that tend to differ between men and women) are more common among men.

Duration of Symptoms Acute presentations (*days to weeks*) of ILD are unusual and are commonly misdiagnosed as more common diseases such as pneumonia, a chronic obstructive pulmonary disease

(COPD) exacerbation, or heart failure. ILDs that can present acutely include eosinophilic pneumonia, acute interstitial pneumonia (AIP), HP, and granulomatosis with polyangiitis (GPA). An acute exacerbation of IPF as the initial presentation of this disease should also be a consideration given its prevalence. ILDs most commonly have a chronic indolent presentation (*months to years*) typified by IPF. However, subacute presentations (*weeks to months*) can occur in most of the ILDs, but in the right context could suggest sarcoidosis, CTD-associated ILD, drug-induced ILD, or COP.

Respiratory Symptoms Progressive dyspnea, most frequently noted with exertion, is the most common complaint in patients presenting with an ILD. Despite this fact, both research studies of general population samples and clinical experiences of asymptomatic patient referrals with abnormal chest CT imaging patterns have also demonstrated that some patients, even those with more extensive disease, may not report dyspnea. Cough, particularly a dry cough, is also common and can be the most prominent symptom in patients with IPF. Cough is often reported in other ILDs, particularly those that have prominent airway involvement including sarcoidosis and HP. Cough with hemoptysis is rare and could suggest an ILD associated with diffuse alveolar hemorrhage (DAH) (e.g., Goodpasture's syndrome), GPA, or LAM. Cough with hemoptysis could also suggest a secondary pulmonary infection that can be seen in patients with traction bronchiectasis and in those receiving immunosuppressive therapy. Chest pain is rare in most of the ILDs with the exception of sarcoidosis where chest discomfort is not uncommon. Fatigue is common to all of the ILDs.

Past Medical History The most pertinent history includes a personal history of a CTD or a history of symptoms commonly associated with a CTD (e.g., Raynaud's phenomena). It is also important to remember that ILD associated with a CTD can be the initial presenting symptom of the disease and can precede the development of additional symptomatology by many years. A history of malignancy is important because some malignancies can be associated with dermatomyositis-associated COP and sarcoid-like reactions. A history of asthma and allergic rhinitis might suggest a diagnosis of eosinophilic GPA.

2192 Medications Many medications have been associated with ILD, and to complicate matters further, many medications commonly used to treat inflammatory and granulomatous lung disease are also associated with ILD development (e.g., methotrexate, azathioprine, rituximab, and the tumor necrosis factor -blocking agents). Specific medications in many classes are also known to cause ILD, including antibiotics (e.g., nitrofurantoin), antiarrhythmics (e.g., amiodarone), and many of the antineoplastic agents (e.g., bleomycin).

Family History A family history of ILD (of almost any type) is important to ascertain. The percentage of pulmonary fibrosis that is familial, as opposed to idiopathic, varies by study, with estimates ranging from <5% to as high as 20%. Despite this variability, most agree that the presence of a close relative with an IIP is among the strongest risk factors for IPF. Family studies have consistently noted familial aggregation of diverse forms of IIP (such as IPF, nonspecific interstitial pneumonia [NSIP], and DIP running in the same family) and, in some cases, other forms of ILD. To date, the most well-replicated genetic factors for pulmonary fibrosis (a promoter variant of a mucin gene [*MUC5B*]) and various genetic determinants known to influence telomere length (e.g., variants in the telomerase reverse transcriptase gene [*TERT*]) (**Chap. 482**) appear to be associated with both familial and idiopathic forms of pulmonary fibrosis similarly.

Social History A history of smoking is nearly always present in some forms of ILD (e.g., respiratory bronchiolitis and desquamative interstitial pneumonia [DIP]—sometimes referred by pathologists jointly as smoking-related ILD) where it is felt to be causative. A history of smoking is also noted in approximately three-quarters of IPF patients. Occupational and environmental exposure histories are also important to obtain as they might identify exposures known to cause pulmonary fibrosis (e.g., significant asbestos exposure) or HP (pigeon breeder's lung).

PHYSICAL EXAMINATION

End-inspiratory fine crackles, or rales, noted at the lung bases are found in most patients with IPF and may be one of the earliest signs of the disease. However, rales are nonspecific and can be found in many forms of ILD and other disorders. Wheezing is uncommon in most forms of ILD but can be present in some disorders, such as sarcoidosis, HP, and eosinophilic GPA. Signs of advanced disease include cyanosis, digital clubbing, and cor pulmonale.

LABORATORY STUDIES

Laboratory studies can be particularly helpful in the workup for an underlying CTD-associated ILD. As noted previously, these tests can reveal the presence of an underlying CTD as the cause of an ILD (e.g., a positive anti-cyclic citrullinated peptide [anti-CCP] antibody for RA) even when no other symptomatology or physical examination findings suggestive of the disorder are present. However, the cost-effectiveness and the extent of laboratory testing that should be ordered in various clinical contexts have yet to be determined (as there is a relatively long list of autoantibody tests that could be ordered).

PULMONARY FUNCTION TESTS

Most forms of ILD will eventually result in a restrictive deficit on pulmonary function testing. A restrictive deficit is typified by a reduced total lung capacity (TLC) and symmetrically reduced measures of forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC). A reduction in the diffusing capacity of the lung for carbon monoxide (DL_{CO}) is also common and may precede a reduction in lung volumes; however, there is more measurement variability in DL_{CO} measurement and the test is less specific for ILD. A reduced FEV₁ to FVC ratio, which is diagnostic of airway obstruction, is unusual in many forms of ILD but can be present as an isolated finding or in conjunction with an additional restrictive deficit in ILDs involving the airways such as sarcoidosis, HP, and LAM. Although pulmonary function testing is rarely diagnostic, reductions in lung function help to characterize the extent of disease, and evidence for decline in repeated measures of pulmonary function (e.g., FVC) has been correlated with an elevated rate of mortality.

CHEST IMAGING STUDIES

Chest X-Ray Findings on CXR can be the first clinical indication that an ILD might be present. For example, enlarged hilar lymph nodes and a pattern of central nodular opacities in the mid to upper lung zones can suggest sarcoidosis. A basilar reticular pattern, with small cystic spaces, in the absence of clinical evidence for heart failure, might suggest IPF. With a few exceptions, CXR alone rarely leads to a specific diagnosis.

Chest CT High-resolution CT (HRCT) chest imaging is now considered to be standard of care in the initial evaluation of a patient with a suspected ILD. HRCT can be diagnostic for some ILDs (e.g., IPF) in the right clinical context and may preclude the need for, and spare the patient the risk of, a lung biopsy. HRCT also helps to define the extent of the ILD, determine the presence of more concerning features suggestive of advanced disease (e.g., honeycombing), provide information on coexisting diseases (e.g., emphysema and lung cancer), and when not diagnostic, provide the most useful locations for obtaining lung biopsy specimens.

LUNG BIOPSY

Fiberoptic Bronchoscopy Bronchoscopy can be helpful in establishing a specific ILD diagnosis, and can help to establish an alternate diagnosis, in select cases. Examination of serial lavage fluid can be helpful in establishing DAH, which can be present in ILDs with vasculitis (e.g., GPA), and in some cases, cellular examination can suggest a specific diagnosis (eosinophilia >25% in chronic eosinophilic pneumonia or fat globules in macrophages in lipoid pneumonia). Transbronchial lung biopsies and lymph node biopsies (in sarcoidosis in particular) can lead to a confident diagnosis in patients with likely granulomatous lung disease (e.g., sarcoidosis and HP). However, in general, bronchoscopically obtained tissue samples are often felt to be insufficient to diagnose most of the IIPs. To date, studies have been mixed on whether bronchoscopically obtained cryobiopsies, which can result in yields larger than those obtained by transbronchial forceps biopsies, could improve the diagnostic yield of bronchoscopy; however, the precise role of cryobiopsies in the diagnostic workup of ILD has yet to be clarified.

Surgical Lung Biopsy A surgically obtained lung biopsy specimen can help solidify the diagnosis of ILD. In many cases, these are now obtained through a video-assisted thoracoscopic (VATS) approach (as compared to an open thoracotomy), which tends to reduce the length of operative times and hospital stays. The diagnostic yield of biopsies tends to be higher if obtained prior to treatment. The desire to obtain a surgical lung biopsy should be weighed against the risks, which can include a short-term mortality rate of as high as 5%. These risks are reported to be higher in biopsies of patients ultimately diagnosed with IPF and in those presenting acutely.

INDIVIDUAL FORMS OF ILD

The ILDs include a diverse group of lung pathologies that can be sub-classified into those disorders of unknown cause (e.g., IIPs) and those of known cause (e.g., sometimes referred to as secondary interstitial pneumonias [CTD-associated ILDs]) (see Fig. 293-1). Although this remains a useful approach to classifying this diverse group of disorders, it is important to recognize that genetic studies are challenging this classic categorization. For example, numerous ILDs commonly listed as having an “unknown cause” have been determined to have significant genetic underpinnings (e.g., IPF and LAM), while the pathophysiologic processes that result in ILDs of “known cause” (e.g., CTD) remain incompletely understood. Diagnosis is based on combined information obtained from a patient’s clinical presentation, measures of pulmonary function, imaging, immune serologies, and histopathology. It is important to remember that prognosis and treatment vary widely by disorder (and disease extent). In some cases, medical therapy that is felt to be effective for some ILDs has been proven to be harmful for others. Medical treatments range from immune modulators to antifibrotic

medications, whereas lung transplantation remains the standard of care for patients with advanced and rapidly progressive ILDs.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

IDIOPATHIC PULMONARY FIBROSIS

Clinical Manifestations IPF is the most common ILD of unknown cause. Prevalence increases with age and is estimated at 50–200:100,000. IPF is commonly diagnosed in the fifth or sixth decade in life, affects men more than women, and is frequently associated with a history of smoking or other environmental exposures. IPF is a variably progressive disease that carries a poor prognosis with an estimated 50% 3- to 5-year survival.

HRCT Image Findings Chest CT findings include subpleural reticulation with a posterior basal predominance usually including more advanced fibrotic features, such as honeycombing and traction bronchiectasis. Collectively, these imaging findings are referred to as a UIP pattern. The presence of extensive ground-glass opacities, bronchovascular changes, micronodules, mosaic attenuation, or an upper lung predominance should raise suspicion for an alternative diagnosis (Fig. 293-2).

Histopathology Diagnostic VATS biopsy findings include subpleural reticulation associated with honeycomb changes and fibroblast foci (subepithelial collections of myofibroblasts and collagen). These

fibrotic changes alternate with areas of preserved normal alveolar architecture consistent with temporal and spatial heterogeneity (Fig. 293-3). Collectively, these pathologic findings are referred to as UIP.

Treatment Historically, IPF was felt to be refractory to medical therapy with lung transplantation the only viable therapeutic option. This dogma changed in 2014 with large clinical trials that demonstrated that antifibrotic therapy (pirfenidone and nintedanib) can slow decline of lung function in IPF patients. Further meta-analyses have suggested that antifibrotic therapy may also improve survival. Trials now suggest that antifibrotic therapy may be broadly effective in other forms of progressive pulmonary fibrosis as well. In contrast, treatment with immunosuppression, which had been commonly prescribed to many IPF patients, has now been demonstrated (in some cases) to be associated with increased morbidity and mortality. Physical therapy and supplemental oxygen, when indicated, can improve exercise tolerance and reduce likelihood of developing pulmonary hypertension. Lung transplantation can extend survival and improve the quality of life in a subset of IPF patients who meet criteria to undergo transplant.

NONSPECIFIC INTERSTITIAL PNEUMONIA

Clinical Manifestations Idiopathic NSIP is a distinct clinical entity with characteristic clinical, radiologic, and pathologic features; however, NSIP is also commonly observed in patients with CTD and less frequently with familial interstitial pneumonia, drug toxicity, and infection. Although the prevalence of NSIP is not well established, it is

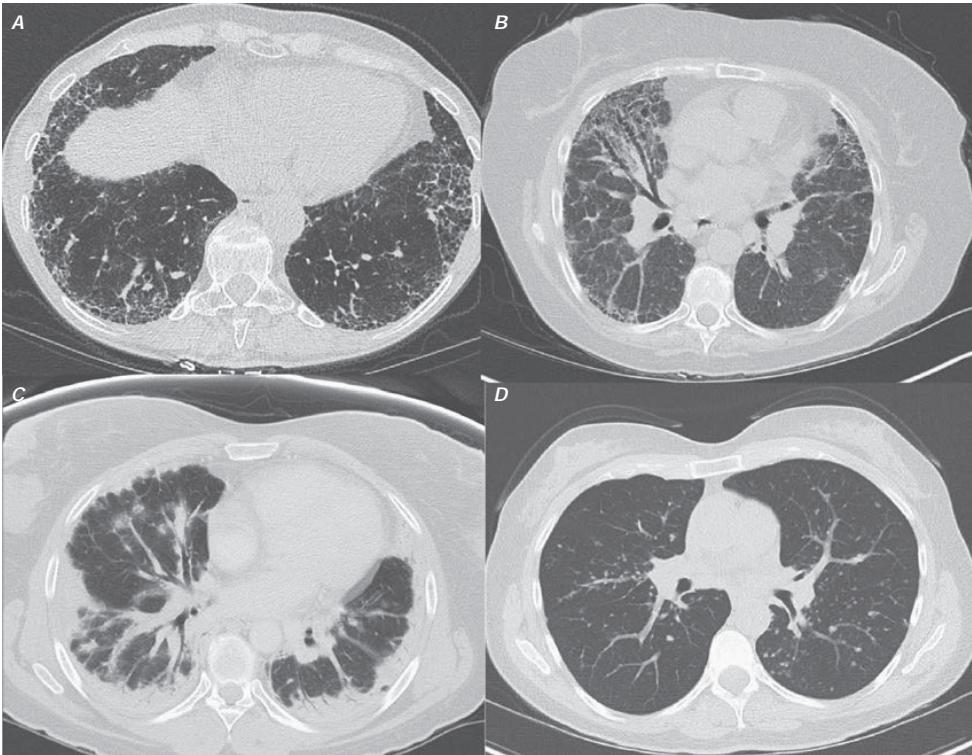


FIGURE 293-2 Chest CT imaging and interstitial lung disease. **A.** Idiopathic pulmonary fibrosis (IPF): Classic findings of IPF (apparent on this image) include a posterior, basilar predominance of subpleural reticular markings and more advanced features of pulmonary fibrosis including traction bronchiectasis and honeycombing. This constellation of findings is often referred to as a usual interstitial pneumonia (UIP) pattern. **B.** Nonspecific interstitial pneumonia (NSIP): Chest CT findings of NSIP can overlap with those of a UIP pattern but tend to include a bilateral, symmetric pattern that presents with a greater percentage of ground-glass opacities than is apparent in a UIP pattern. Additional unique findings include more diffuse imaging abnormalities with a predominance not limited to the lung bases, imaging abnormalities that spare the subpleural regions, and thickening of the bronchovascular bundles (as is apparent in the right mid lung zone on this image). **C.** Cryptogenic organizing pneumonia: Chest CT findings include patchy, sometimes migratory, subpleural consolidative opacities (as is apparent on this image) often with associated ground-glass opacities. Peribronchiolar or perilobular opacities can be present, and sometimes a rim of subpleural sparing (often referred to as a reversed halo or atoll sign) can be seen, which can help to aid in the diagnosis. **D.** Sarcoidosis: Sarcoidosis can present with varied imaging abnormalities, but a pattern of mediastinal and hilar lymphadenopathy with a pattern of reticular-nodular opacities involving the bronchovascular bundles (apparent in this image) are common features. Additional findings can include diffuse small nodules in a miliary pattern, larger nodular opacities, extensive ground-glass infiltrates, and mosaic attenuation suggestive of small airways involvement, and, in more advanced cases, signs of pulmonary fibrosis.

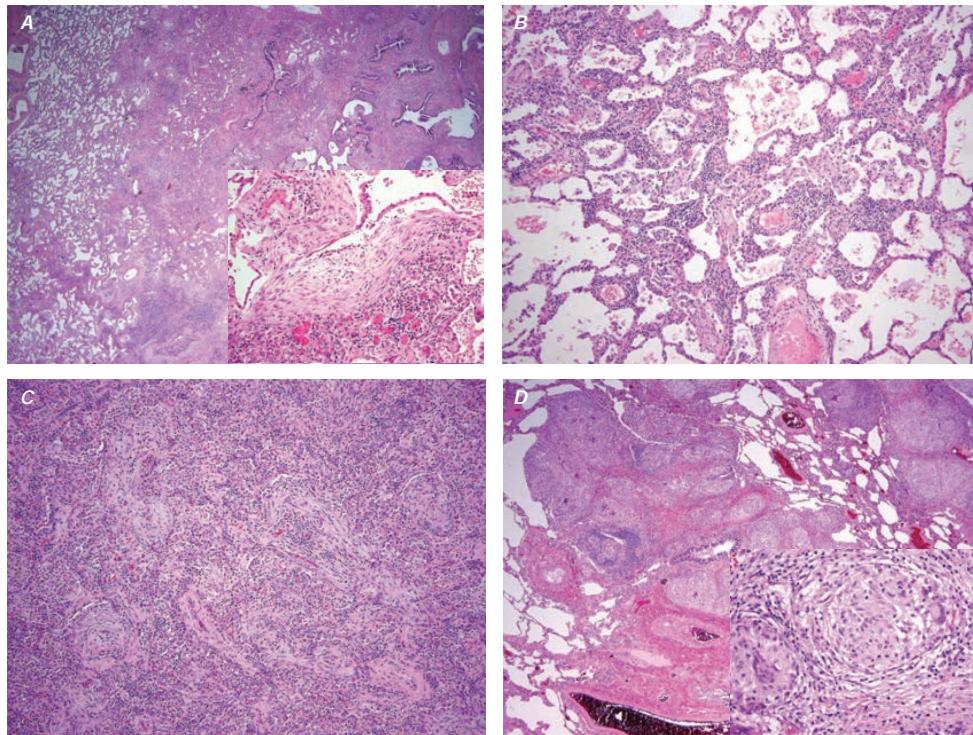


FIGURE 293-3 Histopathology of interstitial lung disease. **A.** Idiopathic pulmonary fibrosis (IPF): Histopathologic findings include subpleural reticulation associated with honeycomb changes alternating with areas of preserved normal lung architecture referred to as temporal and spatial heterogeneity (as is apparent in the low-power image above). Additional important diagnostic findings include fibroblast foci, which are subepithelial collections of myofibroblasts and collagen (as is apparent in the higher-powered inset of this image). Collectively, these pathologic findings are referred to as usual interstitial pneumonia (UIP). **B.** Nonspecific interstitial pneumonia (NSIP): Histopathologic findings of NSIP include varying amounts of interstitial inflammation and fibrosis with a uniform appearance (as is apparent in this image). Honeycomb changes are usually absent and fibroblast foci are rare. NSIP is often referred to histopathologically as being either predominantly cellular or fibrotic. **C.** Cryptogenic organizing pneumonia (COP): Histopathologic findings of COP include patchy regions of organizing pneumonia with granulation tissue that commonly involves the small airways, alveolar ducts, and alveoli with surrounding inflammation that can involve the alveolar walls (as is apparent in this image). **D.** Sarcoidosis: The hallmark histopathologic feature of sarcoidosis is presence of granulomas (as are apparent numerously in the low-powered image and more closely visualized in the higher-powered inset image). Typically, these are referred to as noncaseating, which suggests the absence of necrosis. Caseating granulomas are rare in sarcoid and should prompt additional evaluation for an underlying infection. Because malignancy can result in a granulomatous reaction, it is important to closely survey biopsy specimens with granulomatous involvement for additional signs of malignancy.

commonly diagnosed in nonsmoking females in their fifth decade of life. Positive serologic tests for CTD are frequently observed. Idiopathic NSIP has a relatively good prognosis, with a 5-year survival of >80%; patients with a predominant cellular NSIP pattern have a more favorable prognosis than those with a fibrosing NSIP pattern.

HRCT Image Findings Diffuse subpleural, symmetric, ground-glass, and reticular opacities are common. Volume loss and traction bronchiectasis involving the lower lung zones can also be found. Occasionally subpleural sparing is noted, while peribronchiolar thickening and honeycombing are uncommon.

Histopathology Diagnostic lung biopsy findings include varying amounts of interstitial inflammation and fibrosis with a uniform appearance. Honeycomb changes are usually absent and fibroblast foci are rare. NSIP is often referred to histopathologically as being either predominantly cellular (and potentially more responsive to medical therapy) or fibrotic (and potentially less likely to resolve with medical therapy).

Treatment Pulmonary fibrosis associated with CTD is commonly treated with immunosuppression despite the paucity of randomized clinical trials to demonstrate efficacy. Idiopathic NSIP is often treated with oral steroids (prednisone), cytotoxic agents (mycophenolate, azathioprine, and cyclophosphamide), or biologics (rituximab). Trials now suggest that NSIP patients with progressive pulmonary fibrosis may benefit from antifibrotic therapy. Oxygen therapy, pulmonary rehabilitation, and lung transplantation may be required in patients with progressive disease.

SMOKING-RELATED ILD

Although smoking-related ILDs, including respiratory bronchiolitis with interstitial lung disease (RB-ILD), and DIP are frequently subclassified with the IIPs, these disorders (along with PLCH, an ILD with unique clinical, imaging, and histopathologic manifestations) are commonly felt to be the result of active or prior tobacco smoke exposure. DIP has also been known to occur in children with familial pulmonary fibrosis (FPF). Smokers, particularly elderly smokers, frequently have radiologic (centrilobular) interstitial abnormalities. These interstitial abnormalities are often incidentally found on routine CXR or chest CT studies in asymptomatic or minimally symptomatic individuals. Respiratory bronchiolitis is felt to correlate histopathologically with these imaging findings. However, in some cases, these imaging findings can progress to more advanced radiologic changes where more diffuse signs of interstitial pneumonia tend to be present.

Clinical Manifestations These disorders predominantly occur in active, and in many cases heavy, smokers who are typically between 40 and 50 years of age. In those ultimately diagnosed with RB-ILD or DIP, dyspnea and cough are relatively common and symptomatic wheezing is not rare. The prevalence of smoking-related ILDs is not well understood, but they are generally felt to account for <10% of the IIPs. While there are minimal data on the natural histories and prognoses of these conditions, prolonged survival can be expected in most patients with RB-ILD and death secondary to progressive ILD is felt to be rare.

HRCT Image Findings Prominent and common findings in RB-ILD include central bronchial wall thickening, peripheral bronchial

wall thickening, centrilobular nodules, and ground-glass opacities. Septal lines and a reticular pattern are also not uncommon. Honeycombing is generally felt to be rare (and indicates a worse prognosis). Similar findings are noted in patients with DIP where diffuse (or patchy) bilateral symmetric ground-glass opacities tend to be even more prominent.

Histopathology Common features of RB-ILD include the accumulation of pigmented macrophages within the lumens of respiratory bronchioles and alveolar ducts, accompanied by chronic inflammation of the respiratory bronchiolar walls and both bronchiolar and peribronchiolar alveolar fibrosis causing architectural distortion. These features are patchy and confined to the peribronchiolar region. DIP tends to include similar changes but has a more diffuse pattern characterized by pigmented macrophage accumulation, pneumocyte hyperplasia, and prominent interstitial thickening.

Treatment All patients with smoking-related ILD should be counseled to discontinue smoking and/or encouraged to enroll in a formal smoking cessation program. Small studies have evaluated, and patients are often treated with, immunosuppressive (e.g., prednisone) and cytotoxic (e.g., azathioprine, and cyclophosphamide) agents and, in some cases, bronchodilators. To date, there is no strong evidence that these therapies result in significant improvements in symptoms or measures of pulmonary function or prevent clinical deterioration.

CRYPTOGENIC ORGANIZING PNEUMONIA

Clinical Manifestations COP typically involves patients in their 50–60s and often presents as a subacute flulike illness, with cough, dyspnea, fever, and fatigue. Inspiratory rales are often present on examination, and most patients are noted to have restrictive lung deficits on pulmonary function testing with hypoxemia. COP is commonly mistaken for pneumonia. It is important to note that this syndrome can occur in isolation, can be secondary to an underlying CTD (e.g., polymyositis) or medications, or can result from an underlying malignancy. Laboratory testing for various CTDs is helpful as testing can both be diagnostic and suggest the need for prolonged medical therapy.

HRCT Image Findings The most common imaging findings include patchy, sometimes migratory, subpleural consolidative opacities often with associated ground-glass opacities. Peribronchiolar or perilobular opacities can be present, and sometimes a rim of subpleural sparing (often referred to as a reversed halo or atoll sign) can be seen, which can aid in the diagnosis.

Histopathology Surgical lung biopsy specimens tend to reveal patchy regions of organizing pneumonia with granulation tissue that commonly involves the small airways, alveolar ducts, and alveoli with surrounding inflammation that can involve the alveolar walls (see Fig. 293-3).

Treatment Corticosteroids can result in substantial clinical improvement in many patients but usually need to be continued for at least 6 months as relapse rates are high. Evidence is growing that alternate cytotoxic (e.g., mycophenolate, cyclophosphamide) or biologic (e.g., rituximab) therapies can be helpful in both treating the disease and reducing the need for steroids. In some patients with secondary forms of the disease, long-term therapy may be needed.

ACUTE OR SUBACUTE IIPS

ACUTE INTERSTITIAL PNEUMONIA (HAMMAN-RICH SYNDROME)

Clinical Manifestations AIP is a rare and often fatal lung disorder that is characterized by an acute onset of respiratory distress and hypoxemia. A prodromal period of symptoms consistent with an acute upper respiratory infection is common. The mortality rate within 6 months of presentation can be quite high (>50%), and recurrences are common. In those who recover, lung function improvement can be substantial. AIP can be difficult to distinguish from acute respiratory

distress syndrome (ARDS) and an acute exacerbation of an unsuspected underlying pulmonary fibrotic process.

HRCT Image Findings The most common imaging findings are patchy bilateral ground-glass opacities. Dependent regions of air-space consolidation are also common.

Histopathology Similar to ARDS and acute exacerbations of underlying pulmonary fibrosis, AIP presents histopathologically as diffuse alveolar damage (DAD) demonstrated on a surgical lung biopsy.

Treatment Treatment is mostly supportive and often includes mechanical ventilation. There is no proven drug therapy for AIP. Glucocorticoids are often given, but they are not clearly effective and data on their use in other forms of DAD (e.g., ARDS) is controversial.

ACUTE EXACERBATIONS OF IIPS

Clinical Manifestations Acute exacerbations are not separate disorders, but rather an accelerated phase of lung injury that can occur in any ILD resulting in pulmonary fibrosis. Acute exacerbations are most commonly described and most severe in patients with known IPF. Acute exacerbations are characterized by an acute onset (<30 days) of respiratory distress and hypoxemia occurring in a patient with underlying pulmonary fibrosis not explained by an alternate cause (e.g., pneumonia, left heart failure). Reported mortality rates are very high (>85%), and mean survival periods range from as little as days to months.

HRCT Image Findings The most common imaging findings include patchy bilateral ground-glass opacities and dependent regions of air-space consolidation. Sometimes these new changes can be appreciated on the background of the imaging findings typified by the underlying IIP, although sometimes they obscure the preceding imaging findings.

Histopathology Acute exacerbations of underlying pulmonary fibrosis present histopathologically as DAD, although sometimes organizing pneumonia can also be demonstrated on a surgical lung biopsy.

Treatment Treatment is mostly supportive. Mechanical ventilation, when not being used as a bridge to lung transplantation, is controversial as the survival rate in these patients tends to be poor. There is some evidence that drug therapy (e.g., nintedanib) may reduce the rate of acute exacerbations in patients with IPF. Drug therapy, in the context of an acute exacerbation, is also controversial. Immunosuppressive (e.g., prednisone) and cytotoxic (e.g., cyclophosphamide) therapies are commonly used without proven benefit.

ILD ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

ILD is a common disease manifestation of many CTDs. Disease progression, response to therapy, and survival are variable and associated with specific radiologic and histopathologic patterns. ILD occurs most commonly in patients with scleroderma (systemic sclerosis form, or SSc), RA, polymyositis/dermatomyositis, and less frequently Sjögren's syndrome and systemic lupus erythematosus (SLE). ILD may precede the development of extrapulmonary manifestations of a specific CTD or may present as part of a poorly defined CTD. In rare cases, lung manifestations may be the sole feature of the patient's clinical presentation.

SYSTEMIC SCLEROSIS

Clinical Manifestations (Chap. 360) ILD is the most common pulmonary manifestation of SSc. ILD occurs in ~50% of SSc patients with diffuse disease and in ~30% of patients with limited disease. Pulmonary hypertension can occur separately or concomitantly with ILD and is more frequent in patients with limited SSc.

HRCT Image Findings Similar imaging findings noted in both patients with NSIP and IPF can be present, although findings consistent with COP and DAD may also be present. Additional HRCT findings may include a dilated esophagus and pulmonary artery enlargement.

2196 Histopathology Comparable to the imaging overlap, histopathologic changes commonly noted in patients with NSIP and IPF are frequently identified. Additionally, aspiration related to esophageal dysmotility is common in SSc, and in these patients, histopathologic findings consistent with COP and DAD may be observed.

Treatment Cyclophosphamide has a modest benefit in preservation of lung function and is associated with significant toxicity. Mycophenolate has recently been shown to have similar efficacy and improved tolerability. Clinical trials have demonstrated that antifibrotic therapy (e.g., nintedanib) may benefit patients with systemic sclerosis associated pulmonary fibrosis. Minimizing the risk of reflux by using high-dose proton pump inhibitors or antireflux surgery should be considered in SSc with progressive ILD. Lung transplantation can potentially be offered to select patients without significant aspiration or chest wall restriction.

RHEUMATOID ARTHRITIS

Clinical Manifestations (Chap. 358) A common extraarticular complication of RA is ILD. Although RA is more common in females, RA-ILD is more frequent in males and in patients with a history of tobacco exposure. In a small subset of patients, ILD is the first disease manifestation of RA. Clinically evident RA-ILD occurs in nearly 10% of the RA population; however, up to 40–50% of RA patients have radiologic abnormalities on chest CT, suggesting that ILD in the context of RA may be underdiagnosed.

HRCT Image Findings The most common imaging pattern of ILD in patients with RA is a UIP pattern, although NSIP patterns are not uncommon. There is evidence that survival in patients with RA is decreased in patients with a UIP pattern and among those with more extensive fibrosis in general.

Histopathology Histopathologic findings of UIP and NSIP are most common. Some studies suggest that UIP in the context of RA (as compared to IPF) may present with a reduced number of fibroblastic foci and an increased amount of germinal centers. Comparable to the imaging findings, UIP (and DAD) patterns in patients with RA are associated with reduced survival.

Treatment In contrast with SSc, there are no randomized clinical trials testing the role of immune suppression in RA-ILD. Extrapolating from the scleroderma experience, immunosuppressive (e.g., prednisone) and cytotoxic (e.g., mycophenolate, azathioprine, cyclophosphamide, and calcineurin inhibitors) agents have been used with variable success. Clinical trials testing antifibrotic therapies (pirfenidone and nintedanib) are presently being conducted. Lung transplantation is a viable therapeutic approach for eligible patients with progressive disease that is not responsive to medical therapy.

DERMATOMYOSITIS/POLYMYOSITIS

Clinical Manifestations (Chap. 365) The idiopathic inflammatory myopathies are disorders characterized by immune-mediated destruction and dysfunction of muscle; however, these disorders can affect the skin, joints, cardiovascular system, and lung. The prevalence of ILD associated with inflammatory myopathy varies by report; however, ILD is present in up to 45% of patients with positive anti-synthetase antibodies. The anti-synthetase syndrome is characterized by positive anti-synthetase antibodies, myositis, fever, Raynaud's phenomenon, mechanic's hands, arthritis, and progressive ILD. There is a subset of anti-Jo-1 antibody-positive individuals who can develop a rapidly progressive form of ILD consistent with an acute exacerbation. Some studies have suggested that ILD may be even more common in those with other antibodies (e.g., anti-PL-12). Dermatomyositis/polymyositis can occur as an isolated CTD or as a process associated with an underlying malignancy.

HRCT Image Findings Common imaging patterns of ILD in patients with dermatomyositis/polymyositis include those consistent with NSIP with or without evidence for COP. A UIP pattern can also

occur. Some studies have suggested that a UIP pattern may be more common among those with anti-PL-12 antibodies.

Histopathology The anti-synthetase syndrome is associated with multiple histopathologic subtypes including NSIP, COP, and UIP. DAD, a histopathologic pattern observed in AIP and acute exacerbations, is associated with rapidly progressive ILD in myositis patients.

Treatment Immunosuppressive (e.g., prednisone) and cytotoxic (e.g., mycophenolate, azathioprine, cyclophosphamide, and calcineurin inhibitors) agents are often used in patients with progressive ILD. Some patients (particularly those with less fibrosis) have been noted to have improved or resolved ILD in response to medical therapy. In small studies, relapses have been more common in patients treated with prednisone alone. Patients who fail immune-suppressive therapy can benefit from lung transplantation.

GRANULOMATOUS ILDS

The most common granulomatous ILD is sarcoidosis, a multisystem disorder of unknown cause where lung involvement is often the most dominant feature; sarcoidosis is discussed in Chap. 367. HP, a granulomatous reaction due to inhalation of organic (e.g., bird fancier's lung secondary to exposure to bird feathers) and inorganic (e.g., coal worker's pneumoconiosis secondary to exposure to coal dusts) dusts, is also an important and common cause of ILD and is discussed in Chap. 288.

Granulomatous Vasculitides (See Chap. 64) These disorders are characterized by blood vessels with inflammatory infiltrates and associated granulomatous lesions with or without the presence of tissue necrosis. The lungs are commonly involved, and a unique feature of these disorders is that hemoptysis can be a presenting symptom. Although laboratory testing is often helpful and can provide specific information, biopsies of involved tissue can be essential for making the diagnosis. Many of these disorders include additional systemic manifestations. GPA, also referred to as Wegener's disease, is an example of a granulomatous vasculitis that commonly affects the lung (including inflammatory infiltrates in small to medium-sized vessels), ears, nose, throat, and kidney (resulting in glomerulonephritis). Common imaging abnormalities of GPA include nodules, patchy ground-glass and consolidative opacities that can be migratory, and hilar lymphadenopathy. Eosinophilic GPA (EG; also referred to as Churg-Strauss syndrome) is another example of a granulomatous vasculitis that affects the lung (including eosinophilic infiltrates in small to medium-sized vessels) and can result in numerous clinical manifestations but frequently includes chronic sinusitis, asthma, and peripheral blood eosinophilia. Common imaging abnormalities of EG include peripheral consolidative opacities that can be migratory and small pleural effusions.

GENETICS AND ILD

Studies of genetic epidemiology have led to important insights in our understanding of ILD. First, studies of families with FPF have demonstrated that unique IIPs can cosegregate with specific genetic variants known to be associated with IPF. This suggests that many genetic variants appear to predispose to interstitial lung injury patterns more broadly than to unique diagnoses specifically. Second, most of the genetic variants known to be associated with FPF are also associated with more sporadic forms of the disease. Third, at least one of the genetic factors most strongly associated with FPF and IPF is both common and confers a large increase in the risk of these diseases. At least one copy of a mucin 5B (*MUC5B*) promoter variant is present in ~20% of Caucasian populations and 35–45% of patients with IPF and confers an approximate sixfold increase in the risk of this disease. Fourth, studies of general population samples demonstrate that imaging abnormalities suggestive of an early stage of pulmonary fibrosis in research participants without known ILD are not uncommon (occurring in ~7–9% of adults) and are also associated with the same genetic variants known to be associated with IPF (e.g., the *MUC5B* promoter variant). This latter finding suggests a path forward toward an early detection of IPF. Additional genetic findings demonstrating replicable associations with pulmonary fibrosis include numerous genetic variants in, and

adjacent to, genes known to be involved in the regulation of telomere length (e.g., the *TERT* gene, the telomerase RNA component [*TERC*] gene, and the regulator of telomere elongation helicase 1 [*RTEL1*] gene) and surfactant protein genes (e.g., surfactant protein A2 [*SFTPA2*] gene) (Chap. 482).

Genetic studies have also provided some insights into other forms of ILD. Genome-wide association studies of sarcoidosis have demonstrated numerous variants in genes and in genomic regions that are associated with the disease. Some of these disease-associated variants in sarcoidosis fall in human leukocyte antigen (*HLA*) regions, in regions of genes involved in immune regulation (e.g., interleukin 12B [*IL12B*]), and in regions of genes that are less well understood (butyrophilin-like 2 [*BTNL2*]) but also appear to be involved in T-cell activation. LAM is often associated with genetic variants in the tuberous sclerosis complex genes (e.g., *TSC1* and *TSC2*), consistent with the known evidence that this disease can occur in isolation but also in patients with known tuberous sclerosis. Many genetic factors for rare diseases such as Hermansky-Pudlak syndrome (a rare autosomal recessive disorder that results in pulmonary fibrosis but also includes oculocutaneous albinism, bleeding diatheses, and horizontal nystagmus) have also been discovered (e.g., *HSP1*, and *HSP3-7*).

GLOBAL CONSIDERATIONS

The prevalence, clinical presentation, and natural history of most ILDs in European countries resemble those described in the United States. However, as expected, there is growing evidence for racial differences in clinical (rate of acute exacerbations) and genetic (*MUC5B*) attributes between Caucasian and Asian populations. To date, there are limited data on the prevalence of ILD in Hispanics, subjects of African descent, and many other ethnic groups.

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294 Disorders of the Pleura

Richard W. Light

PLEURAL EFFUSION

The pleural space lies between the lung and the chest wall and normally contains a very thin layer of fluid, which serves as a coupling system. A pleural effusion is present when there is an excess quantity of fluid in the pleural space.

Etiology Pleural fluid accumulates when pleural fluid formation exceeds pleural fluid absorption. Normally, fluid enters the pleural

space from the capillaries in the parietal pleura and is removed via the lymphatics in the parietal pleura. Fluid also can enter the pleural space from the interstitial spaces of the lung via the visceral pleura or from the peritoneal cavity via small holes in the diaphragm. The lymphatics have the capacity to absorb 20 times more fluid than is formed normally. Accordingly, a pleural effusion may develop when there is excess pleural fluid formation (from the interstitial spaces of the lung, the parietal pleura, or the peritoneal cavity) or when there is decreased fluid removal by the lymphatics.

Diagnostic Approach Patients suspected of having a pleural effusion should undergo chest imaging to diagnose its extent. Chest ultrasound has replaced the lateral decubitus x-ray in the evaluation of suspected pleural effusions and as a guide to thoracentesis. When a patient is found to have a pleural effusion, an effort should be made to determine the cause (Fig. 294-1). The first step is to determine whether the effusion is a transudate or an exudate. A *transudative pleural effusion* occurs when *systemic* factors that influence the formation and absorption of pleural fluid are altered. The leading causes of transudative pleural

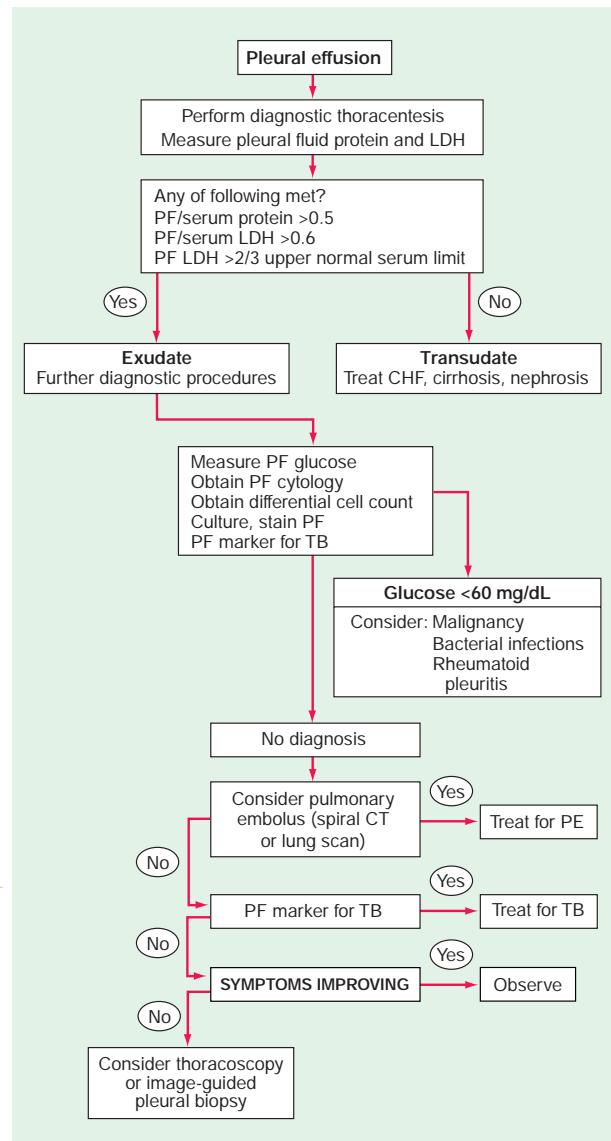


FIGURE 294-1 Approach to the diagnosis of pleural effusions. CHF, congestive heart failure; CT, computed tomography; LDH, lactate dehydrogenase; PE, pulmonary embolism; PF, pleural fluid; TB, tuberculosis.

*Deceased.

2198 effusions in the United States are left ventricular failure and cirrhosis. An *exudative pleural effusion* occurs when *local factors* that influence the formation and absorption of pleural fluid are altered. The leading causes of exudative pleural effusions are bacterial pneumonia, malignancy, viral infection, and pulmonary embolism. The primary reason for making this differentiation is that additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none:

1. Pleural fluid protein/serum protein >0.5
2. Pleural fluid LDH/serum LDH >0.6
3. Pleural fluid LDH more than two-thirds the normal upper limit for serum

These criteria misidentify ~25% of transudates as exudates. If one or more of the exudative criteria are met and the patient is clinically thought to have a condition producing a transudative effusion, the difference between the protein levels in the serum and the pleural fluid should be measured. If this gradient is >31 g/L (3.1 g/dL), the exudative categorization by these criteria can be ignored because almost all such patients have a transudative pleural effusion.

If a patient has an exudative pleural effusion, the following tests on the pleural fluid should be obtained: description of the appearance of the fluid, glucose level, differential cell count, microbiologic studies, and cytology.

Effusion Due to Heart Failure The most common cause of pleural effusion is left ventricular failure. The effusion occurs because the increased amounts of fluid in the lung interstitial spaces exit in part across the visceral pleura; this overwhelms the capacity of the lymphatics in the parietal pleura to remove fluid. In patients with heart failure, a diagnostic thoracentesis should be performed if the effusions are not bilateral and comparable in size, if the patient is febrile, or if the patient has pleuritic chest pain to verify that the patient has a transudative effusion. Otherwise, the patient's heart failure is treated. If the effusion persists despite therapy, a diagnostic thoracentesis should be performed. A pleural fluid N-terminal pro-brain natriuretic peptide (NT-proBNP) level >1500 pg/mL is virtually diagnostic of an effusion that is secondary to congestive heart failure.

Hepatic Hydrothorax Pleural effusions occur in ~5% of patients with cirrhosis and ascites. The predominant mechanism is the direct movement of peritoneal fluid through small openings in the diaphragm into the pleural space. The effusion is usually right-sided and frequently is large enough to produce severe dyspnea.

Parapneumonic Effusion Parapneumonic effusions are associated with bacterial pneumonia, lung abscess, or bronchiectasis and are probably the most common cause of exudative pleural effusion in the United States. *Empyema* refers to a grossly purulent effusion.

Patients with aerobic bacterial pneumonia and pleural effusion present with an acute febrile illness consisting of chest pain, sputum production, and leukocytosis. Patients with anaerobic infections present with a subacute illness with weight loss, a brisk leukocytosis, mild anemia, and a history of some factor that predisposes them to aspiration.

The possibility of a parapneumonic effusion should be considered whenever a patient with bacterial pneumonia is initially evaluated. The presence of free pleural fluid can be demonstrated with a lateral decubitus radiograph, computed tomography (CT) of the chest, or ultrasound. If the free fluid separates the lung from the chest wall by >10 mm, a therapeutic thoracentesis should be performed. Factors indicating the likely need for a procedure more invasive than a thoracentesis (in increasing order of importance) include the following:

1. Loculated pleural fluid
2. Pleural fluid pH <7.20
3. Pleural fluid glucose <3.3 mmol/L (<60 mg/dL)
4. Positive Gram stain or culture of the pleural fluid
5. Presence of gross pus in the pleural space

If the fluid recurs after the initial therapeutic thoracentesis and if any of these characteristics is present, a repeat thoracentesis should be performed. If the fluid cannot be completely removed with the therapeutic thoracentesis, consideration should be given to inserting a chest tube and instilling the combination of a fibrinolytic agent (e.g., tissue plasminogen activator, 10 mg) and deoxyribonuclease (5 mg) or performing a thoracoscopy with the breakdown of adhesions. Decortication should be considered when these measures are ineffective.

Effusion Secondary to Malignancy Malignant pleural effusions secondary to metastatic disease are the second most common type of exudative pleural effusion. The three tumors that cause ~75% of all malignant pleural effusions are lung carcinoma, breast carcinoma, and lymphoma. Most patients complain of dyspnea, which is frequently out of proportion to the size of the effusion. The pleural fluid is an exudate, and its glucose level may be reduced if the tumor burden in the pleural space is high.

The diagnosis usually is made via cytology of the pleural fluid. If the initial cytologic examination is negative, thoracoscopy is the best next procedure if malignancy is strongly suspected. At the time of thoracoscopy, a procedure such as pleural abrasion should be performed to effect a pleurodesis. An alternative to thoracoscopy is CT- or ultrasound-guided needle biopsy of pleural thickening or nodules. Patients with a malignant pleural effusion are treated symptomatically for the most part, since the presence of the effusion indicates disseminated disease and most malignancies associated with pleural effusion are not curable with chemotherapy. The only symptom that can be attributed to the effusion itself is dyspnea. If the patient's lifestyle is compromised by dyspnea and if the dyspnea is relieved with a therapeutic thoracentesis, one of the following procedures should be considered: (1) insertion of a small indwelling catheter or (2) tube thoracostomy with the instillation of a sclerosing agent such as doxycycline (500 mg).

Mesothelioma Malignant mesotheliomas are primary tumors that arise from the mesothelial cells that line the pleural cavities; most are related to asbestos exposure. Patients with mesothelioma present with chest pain and shortness of breath. The chest radiograph reveals a pleural effusion, generalized pleural thickening, and a shrunken hemithorax. The diagnosis is usually established with image-guided needle biopsy or thoracoscopy (Fig. 294-2).

Effusion Secondary to Pulmonary Embolism The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion is pulmonary embolism. Dyspnea is the most common symptom. The pleural fluid is almost always an exudate. The diagnosis is established by spiral CT scan or pulmonary arteriography (Chap. 279). Treatment of a patient with a pleural effusion secondary to pulmonary embolism is the same as it is

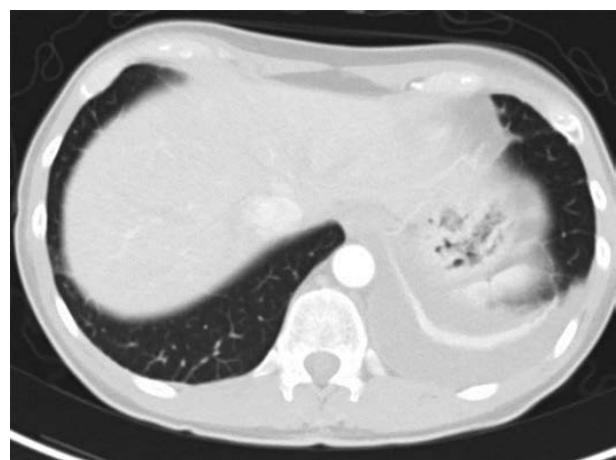


FIGURE 294-2 CT scan from a patient with mesothelioma demonstrating a mass in the left lung, a pleural effusion, pleural thickening, and a shrunken hemithorax.

for any patient with pulmonary emboli. If the pleural effusion increases in size after anticoagulation, the patient probably has recurrent emboli or another complication, such as a hemothorax or a pleural infection.

Tuberculous Pleuritis (See also Chap. 178) In many parts of the world, the most common cause of an exudative pleural effusion is tuberculosis (TB), but tuberculous effusions are relatively uncommon in the United States. Tuberculous pleural effusions usually are associated with primary TB and are thought to be due primarily to a hypersensitivity reaction to tuberculous protein in the pleural space. Patients with tuberculous pleuritis present with fever, weight loss, dyspnea, and/or pleuritic chest pain. The pleural fluid is an exudate with predominantly small lymphocytes. The diagnosis is established by demonstrating high levels of TB markers in the pleural fluid (adenosine deaminase >40 IU/L or interferon ≥ 140 pg/mL). Alternatively, the diagnosis can be established by culture of the pleural fluid, needle biopsy of the pleura, or thoracoscopy. The recommended treatments of pleural and pulmonary TB are identical (Chap. 178).

Effusion Secondary to Viral Infection Viral infections are probably responsible for a sizable percentage of undiagnosed exudative pleural effusions. In many series, no diagnosis is established for ~20% of exudative effusions, and these effusions resolve spontaneously with no long-term residua. The importance of these effusions is that one should not be too aggressive in trying to establish a diagnosis for the undiagnosed effusion, particularly if the patient is improving clinically.

Chylothorax A chylothorax occurs when the thoracic duct is disrupted and chyle accumulates in the pleural space. The most common cause of chylothorax is trauma (most frequently thoracic surgery), but it also may result from tumors in the mediastinum. Patients with chylothorax present with dyspnea, and a large pleural effusion is present on the chest radiograph. Thoracentesis reveals milky fluid, and biochemical analysis reveals a triglyceride level that exceeds 1.2 mmol/L (110 mg/dL). Patients with chylothorax and no obvious trauma should have a lymphangiogram and a mediastinal CT scan to assess the mediastinum for lymph nodes. The treatment of choice for most chylothoraces is insertion of a chest tube plus the administration of octreotide. If these modalities fail, percutaneous transabdominal thoracic duct blockage effectively controls most chylothoraces. An alternative treatment is ligation of the thoracic duct. Patients with chylothoraces should not undergo prolonged tube thoracostomy with chest tube drainage because this will lead to malnutrition and immunologic incompetence.

Hemothorax When a diagnostic thoracentesis reveals bloody pleural fluid, a hematocrit should be obtained on the pleural fluid. If the hematocrit is more than one-half of that in the peripheral blood, the patient is considered to have a hemothorax. Most hemothoraces are the result of trauma; other causes include rupture of a blood vessel or tumor. Most patients with hemothorax should be treated with tube thoracostomy, which allows continuous quantification of bleeding. If the bleeding emanates from a laceration of the pleura, apposition of the two pleural surfaces is likely to stop the bleeding. If the pleural hemorrhage exceeds 200 mL/h, consideration should be given to angiographic coil embolization, thoracoscopy, or thoracotomy.

Miscellaneous Causes of Pleural Effusion There are many other causes of pleural effusion (Table 294-1). Key features of some of these conditions are as follows: If the pleural fluid amylase level is elevated, the diagnosis of esophageal rupture or pancreatic disease is likely. If the patient is febrile, has predominantly polymorphonuclear cells in the pleural fluid, and has no pulmonary parenchymal abnormalities, an intraabdominal abscess should be considered.

The diagnosis of an asbestos pleural effusion is one of exclusions. Benign ovarian tumors can produce ascites and a pleural effusion (Meigs' syndrome), as can the ovarian hyperstimulation syndrome. Several drugs can cause pleural effusion; the associated fluid is usually eosinophilic. Pleural effusions commonly occur after coronary artery bypass surgery. Effusions occurring within the first weeks are

TABLE 294-1 Differential Diagnoses of Pleural Effusions

Transudative Pleural Effusions

1. Congestive heart failure
2. Cirrhosis
3. Nephrotic syndrome
4. Peritoneal dialysis
5. Superior vena cava obstruction
6. Myxedema
7. Urinothorax

Exudative Pleural Effusions

1. Neoplastic diseases
 - a. Metastatic disease
 - b. Mesothelioma
2. Infectious diseases
 - a. Bacterial infections
 - b. Tuberculosis
 - c. Fungal infections
 - d. Viral infections
 - e. Parasitic infections
3. Pulmonary embolization
4. Gastrointestinal disease
 - a. Esophageal perforation
 - b. Pancreatic disease
 - c. Intraabdominal abscesses
 - d. Diaphragmatic hernia
 - e. After abdominal surgery
 - f. Endoscopic variceal sclerotherapy
 - g. After liver transplant
5. Collagen vascular diseases
 - a. Rheumatoid pleuritis
 - b. Systemic lupus erythematosus
 - c. Drug-induced lupus
 - d. Sjögren syndrome
 - e. Granulomatosis with polyangiitis (Wegener)
 - f. Churg-Strauss syndrome
6. Post-coronary artery bypass surgery
7. Asbestos exposure
8. Sarcoidosis
9. Uremia
10. Meigs' syndrome
11. Yellow nail syndrome
12. Drug-induced pleural disease
 - a. Nitrofurantoin
 - b. Dantrolene
 - c. Methysergide
 - d. Bromocriptine
 - e. Procarbazine
 - f. Amiodarone
 - g. Dasatinib
13. Trapped lung
14. Radiation therapy
15. Post-cardiac injury syndrome
16. Hemothorax
17. Iatrogenic injury
18. Ovarian hyperstimulation syndrome
19. Pericardial disease
20. Chylothorax

typically left-sided and bloody, with large numbers of eosinophils, and respond to one or two therapeutic thoracenteses. Effusions occurring after the first few weeks are typically left-sided and clear yellow, with predominantly small lymphocytes, and tend to recur. Other medical

2200 manipulations that induce pleural effusions include abdominal surgery; radiation therapy; liver, lung, or heart transplantation; and the intravascular insertion of central lines.

PNEUMOTHORAX

Pneumothorax is the presence of gas in the pleural space. A *spontaneous pneumothorax* is one that occurs without antecedent trauma to the thorax. A *primary spontaneous pneumothorax* occurs in the absence of underlying lung disease, whereas a *secondary pneumothorax* occurs in its presence. A *traumatic pneumothorax* results from penetrating or nonpenetrating chest injuries. A *tension pneumothorax* is a pneumothorax in which the pressure in the pleural space is positive throughout the respiratory cycle.

Primary Spontaneous Pneumothorax Primary spontaneous pneumothoraces are usually due to rupture of apical pleural blebs, small cystic spaces that lie within or immediately under the visceral pleura. Primary spontaneous pneumothoraces occur almost exclusively in smokers; this suggests that these patients have subclinical lung disease. Approximately one-half of patients with an initial primary spontaneous pneumothorax will have a recurrence. The initial recommended treatment for primary spontaneous pneumothorax is simple aspiration. If the lung does not expand with aspiration or if the patient has a recurrent pneumothorax, thoracoscopy with stapling of blebs and pleural abrasion is indicated. Thoracoscopy or thoracotomy with pleural abrasion is almost 100% successful in preventing recurrences.

Secondary Pneumothorax Most secondary pneumothoraces are due to chronic obstructive pulmonary disease, but pneumothoraces have been reported with virtually every lung disease. Pneumothorax in patients with lung disease is more life-threatening than it is in normal individuals because of the lack of pulmonary reserve in these patients. Nearly all patients with secondary pneumothorax should be treated with tube thoracostomy. Most should also be treated with thoracoscopy or thoracotomy with the stapling of blebs and pleural abrasion. If the patient is not a good operative candidate or refuses surgery, pleurodesis should be attempted by the intrapleural injection of a sclerosing agent such as doxycycline.

Traumatic Pneumothorax Traumatic pneumothoraces can result from both penetrating and nonpenetrating chest trauma. Traumatic pneumothoraces should be treated with tube thoracostomy unless they are very small. If a hemopneumothorax is present, one chest tube should be placed in the superior part of the hemithorax to evacuate the air and another should be placed in the inferior part of the hemithorax to remove the blood. Iatrogenic pneumothorax is a type of traumatic pneumothorax that is becoming more common. The leading causes are transthoracic needle aspiration, thoracentesis, and the insertion of central intravenous catheters. Most can be managed with supplemental oxygen or aspiration, but if these measures are unsuccessful, a tube thoracostomy should be performed.

Tension Pneumothorax This condition usually occurs during mechanical ventilation or resuscitative efforts. The positive pleural pressure is life-threatening both because ventilation is severely compromised and because the positive pressure is transmitted to the mediastinum, resulting in decreased venous return to the heart and reduced cardiac output.

Difficulty in ventilation during resuscitation or high peak inspiratory pressures during mechanical ventilation strongly suggest the diagnosis. The diagnosis is made by physical examination showing an enlarged hemithorax with no breath sounds, hyperresonance to percussion, and shift of the mediastinum to the contralateral side. Tension pneumothorax must be treated as a medical emergency. If the tension in the pleural space is not relieved, the patient is likely to die from inadequate cardiac output or marked hypoxemia. A large-bore needle should be inserted into the pleural space through the second anterior intercostal space. If large amounts of gas escape from the needle after

insertion, the diagnosis is confirmed. The needle should be left in place until a thoracostomy tube can be inserted.

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Disorders of the Mediastinum

Richard W. Light



The mediastinum is the region between the pleural sacs. It is separated into three compartments (Table 295-1). The *anterior mediastinum* extends from the sternum anteriorly to the pericardium and brachiocephalic vessels posteriorly. It contains the thymus gland, the anterior mediastinal lymph nodes, and the internal mammary arteries and veins. The *middle mediastinum* lies between the anterior and posterior mediastina and contains the heart; the ascending and transverse arches of the aorta; the venae cavae; the brachiocephalic arteries and veins; the phrenic nerves; the trachea, the main bronchi, and their contiguous lymph nodes; and the pulmonary arteries and veins. The *posterior mediastinum* is bounded by the pericardium and trachea anteriorly and the vertebral column posteriorly. It contains the descending thoracic aorta, the esophagus, the thoracic duct, the azygos and hemiazygos veins, and the posterior group of mediastinal lymph nodes.

MEDIASTINAL MASSES

The first step in evaluating a mediastinal mass is to place it in one of the three mediastinal compartments, since each has different characteristic lesions (Table 295-1).

Computed tomography (CT) scanning is the most valuable imaging technique for evaluating mediastinal masses and is the only imaging technique that should be done in most instances. Barium studies of the gastrointestinal tract are indicated in many patients with posterior mediastinal lesions, because hernias, diverticula, and achalasia are readily diagnosed in this manner. An iodine-131 scan can efficiently establish the diagnosis of intrathoracic goiter.

A definite diagnosis can be obtained with mediastinoscopy or anterior mediastinotomy in many patients with masses in the anterior or middle mediastinal compartments. A diagnosis can be established without thoracotomy via percutaneous fine-needle aspiration biopsy or endoscopic transesophageal or endobronchial ultrasound-guided biopsy of mediastinal masses in most cases. An alternative way to establish the diagnosis is video-assisted thoracoscopy. In many cases, the diagnosis can be established and the mediastinal mass removed with video-assisted thoracoscopy.

ACUTE MEDIASTINITIS

Cases of acute mediastinitis are usually due to esophageal perforation, occur after median sternotomy for cardiac surgery, or are infections descending from the neck, oral cavity, or facial area. Patients with

*Deceased.

TABLE 295-1 The Three Compartments of the Mediastinum

	ANTERIOR COMPARTMENT	MIDDLE COMPARTMENT	POSTERIOR COMPARTMENT
Anatomical boundaries	Manubrium and sternum anteriorly, pericardium, aorta, and brachiocephalic vessels posteriorly	Anterior mediastinum anteriorly, posterior mediastinum posteriorly	Pericardium and trachea anteriorly; vertebral column posteriorly
Contents	Thymus gland, anterior mediastinal lymph nodes, internal mammary arteries, and veins	Pericardium, heart, ascending and transverse arch of aorta, superior and inferior vena cavae, brachiocephalic arteries and veins, phrenic nerves, trachea, and main bronchi and their contiguous lymph nodes, pulmonary arteries, and veins	Descending thoracic aorta, esophagus, thoracic duct, azygos and hemiazygos veins, sympathetic chains, and the posterior group of mediastinal lymph nodes
Common abnormalities	Thymoma, lymphomas, teratomatous neoplasms, thyroid masses, parathyroid masses, mesenchymal tumors, giant lymph node hyperplasia, hernia through foramen of Morgagni	Metastatic lymph node enlargement, granulomatous lymph node enlargement, pleuropericardial cysts, bronchogenic cysts, masses of vascular origin	Neurogenic tumors, meningocele, meningomyelocele, gastroenteric cysts, esophageal diverticula, hernia through foramen of Bochdalek, extramedullary hematopoiesis

esophageal rupture are acutely ill with chest pain and dyspnea due to the mediastinal infection. The esophageal rupture can occur spontaneously or as a complication of esophagoscopy or the insertion of a Blakemore tube. Appropriate treatment consists of exploration of the mediastinum with primary repair of the esophageal tear and drainage of the pleural space and the mediastinum.

The incidence of mediastinitis after median sternotomy is 0.4–5.0%. Patients most commonly present with wound drainage. Other presentations include sepsis and a widened mediastinum. The diagnosis usually is established with mediastinal needle aspiration. Treatment includes immediate drainage, debridement, and parenteral antibiotic therapy, but the mortality rate still exceeds 20%.

CHRONIC MEDIASTINITIS

The spectrum of chronic mediastinitis ranges from granulomatous inflammation of the lymph nodes in the mediastinum to fibrosing mediastinitis. Most cases are due to histoplasmosis or tuberculosis, but sarcoidosis, silicosis, and other fungal diseases are at times causative. Patients with granulomatous mediastinitis are usually asymptomatic. Those with fibrosing mediastinitis usually have signs of compression of a mediastinal structure such as the superior vena cava or large airways, phrenic or recurrent laryngeal nerve paralysis, or obstruction of the pulmonary artery or proximal pulmonary veins. If veins or arteries are involved, the placement of stents has relieved the symptoms in many patients.

PNEUMOMEDIASTINUM

In this condition, there is gas in the interstices of the mediastinum. The three main causes are (1) alveolar rupture with dissection of air into the mediastinum; (2) perforation or rupture of the esophagus, trachea, or main bronchi; and (3) dissection of air from the neck or the abdomen into the mediastinum. Typically, there is severe substernal chest pain with or without radiation into the neck and arms. The physical examination usually reveals subcutaneous emphysema in the suprasternal notch and *Hamman's sign*, which is a crunching or clicking noise synchronous with the heartbeat and is best heard in the left lateral decubitus position. The diagnosis is confirmed with the chest radiograph. Usually no treatment is required, but the mediastinal air will be absorbed faster if the patient inspires high concentrations of oxygen. If mediastinal structures are compressed, the compression can be relieved with needle aspiration.

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Disorders of Ventilation

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DEFINITION AND PHYSIOLOGY

In health, the arterial level of carbon dioxide (PaCO_2) is maintained between 37 and 43 mmHg at sea level. All disorders of ventilation result in abnormal measurements of PaCO_2 . This chapter reviews chronic ventilatory disorders.

The continuous production of carbon dioxide (CO_2) by cellular metabolism necessitates its efficient elimination by the respiratory system. The relationship between CO_2 production and PaCO_2 is described by the equation: $\text{PaCO}_2 = (k)(\dot{\text{VCO}}_2)/\dot{\text{VA}}$, where $\dot{\text{VCO}}_2$ represents the carbon dioxide production, k is a constant, and $\dot{\text{VA}}$ is fresh gas alveolar ventilation (Chap. 285). $\dot{\text{VA}}$ can be calculated as minute ventilation \times $(1 - \text{Vd}/\text{Vt})$, where the dead space fraction Vd/Vt represents the portion of a tidal breath that remains within the conducting airways at the conclusion of inspiration and so does not contribute to alveolar ventilation. As such, all disturbances of PaCO_2 must reflect altered CO_2 production, minute ventilation, or dead space fraction.

Diseases that alter $\dot{\text{VCO}}_2$ are often acute (e.g., sepsis, burns, or pyrexia), and their contribution to ventilatory abnormalities and/or respiratory failure is reviewed elsewhere. Chronic ventilatory disorders typically involve inappropriate levels of minute ventilation or increased dead space fraction. Characterization of these disorders requires a review of the normal respiratory cycle.

The spontaneous cycle of inspiration and expiration is automatically generated in the brainstem. Two groups of neurons located within the medulla are particularly important: the dorsal respiratory group (DRG) and the ventral respiratory column (VRC). These neurons have widespread projections including the descending projections into the contralateral spinal cord where they perform many functions. They initiate activity in the phrenic nerve/diaphragm, project to the upper airway muscle groups and spinal respiratory neurons, and innervate the intercostal and abdominal muscles that participate in normal respiration. The DRG acts as the initial integration site for many of the afferent nerves relaying information about Pao_2 , PaCO_2 , pH, and blood pressure from the carotid and aortic chemoreceptors and baroreceptors to the central nervous system (CNS). In addition, the vagus nerve relays information from stretch receptors and juxtapulmonary-capillary receptors in the lung parenchyma and chest wall to the DRG. The respiratory rhythm is generated within the VRC as well as the more rostrally located parafacial respiratory group (pFRG), which is particularly important for the generation of active expiration. One particularly important area within the VRC is the so-called pre-Bötzinger complex. This area is responsible for the generation of various forms

2202 of inspiratory activity, and lesioning of the pre-Bötzinger complex leads to the complete cessation of breathing. The neural output of these medullary respiratory networks can be voluntarily suppressed or augmented by input from higher brain centers and the autonomic nervous system. During normal sleep, there is an attenuated response to hypercapnia and hypoxemia, resulting in mild nocturnal hypoventilation that corrects upon awakening.

Once neural input has been delivered to the respiratory pump muscles, normal gas exchange requires an adequate amount of respiratory muscle strength to overcome the elastic and resistive loads of the respiratory system (Fig. 296-1A) (also see Chap. 285). In health,

the strength of the respiratory muscles readily accomplishes this, and normal respiration continues indefinitely. Reduction in respiratory drive or neuromuscular competence or substantial increase in respiratory load can diminish minute ventilation, resulting in hypercapnia (Fig. 296-1B). Alternatively, if normal respiratory muscle strength is coupled with excessive respiratory drive, then alveolar hyperventilation ensues and leads to hypoxemia (Fig. 296-1C).

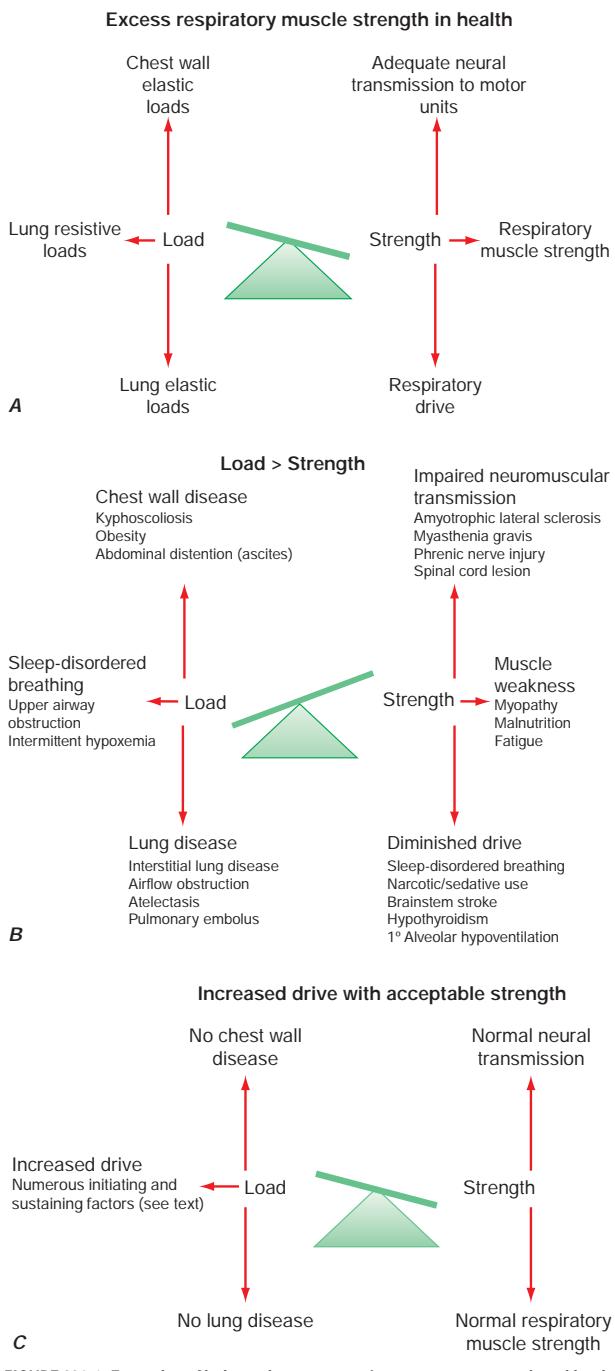


FIGURE 296-1 Examples of balance between respiratory system strength and load.
A. Excess respiratory muscle strength in health. B. Load greater than strength.
C. Increased drive with acceptable strength.

Hypoventilation

CLINICAL FEATURES

Diseases that reduce minute ventilation or increase dead space fall into four major categories: parenchymal lung and chest wall disease, sleep-disordered breathing, neuromuscular disease, and respiratory drive disorders (Fig. 296-1B). The clinical manifestations of hypoventilation syndromes are nonspecific (Table 296-1) and vary depending on the severity of hypoventilation, the rate at which hypercapnia develops, the degree of compensation for respiratory acidosis, and the underlying disorder. Patients with parenchymal lung or chest wall disease typically present with shortness of breath and diminished exercise tolerance. Episodes of increased dyspnea and sputum production are hallmarks of obstructive lung diseases such as chronic obstructive pulmonary disease (COPD), whereas progressive dyspnea and cough are common in interstitial lung diseases. Excessive daytime somnolence, poor-quality sleep, and snoring are common among patients with sleep-disordered breathing. Sleep disturbance and orthopnea are also described in neuromuscular disorders. As neuromuscular weakness progresses, the respiratory muscles, including the diaphragm, are placed at a mechanical disadvantage in the supine position due to the upward movement of the abdominal contents. New-onset orthopnea is frequently a sign of reduced respiratory muscle force generation. More commonly, however, extremity weakness or bulbar symptoms develop prior to sleep disturbance in neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) or muscular dystrophy. Patients with respiratory drive disorders do not have symptoms distinguishable from other causes of chronic hypoventilation.

The clinical course of patients with chronic hypoventilation from neuromuscular or chest wall disease follows a characteristic sequence: an asymptomatic stage where daytime PaCO_2 and Paco_2 are normal followed by nocturnal hypoventilation, initially during rapid eye movement (REM) sleep and later in non-REM sleep. Finally, if vital capacity drops further, daytime hypercapnia develops. Symptoms can develop at any point along this time course and often depend on the pace of respiratory muscle functional decline. Regardless of cause, the hallmark of all alveolar hypoventilation syndromes is an increase in alveolar PCO_2 (PAco_2) and therefore in Paco_2 . The resulting respiratory acidosis eventually leads to a compensatory increase in plasma bicarbonate concentration. The increase in Paco_2 results in an obligatory decrease in PAO_2 , often resulting in hypoxemia. If severe, the hypoxemia manifests clinically as cyanosis and can stimulate erythropoiesis and thus induce secondary erythrocytosis. The combination of chronic hypoxemia and hypercapnia may also induce pulmonary vasoconstriction, leading eventually to pulmonary hypertension, right ventricular hypertrophy, and right heart failure.

DIAGNOSIS

Elevated serum bicarbonate (i.e., total serum CO_2 , which equals calculated bicarbonate plus dissolved CO_2) in the absence of volume depletion is suggestive of hypoventilation. However, it is important to point

TABLE 296-1 Signs and Symptoms of Hypoventilation

Dyspnea during activities of daily living
Orthopnea in diseases affecting diaphragm function
Poor-quality sleep
Daytime hypersomnolence
Early morning headaches
Anxiety
Impaired cough in neuromuscular diseases

out that a serum bicarbonate level <27 mmol/L in the setting of normal renal function makes the diagnosis of hypoventilation very unlikely. By contrast, a serum bicarbonate level >27 mmol/L should trigger clinicians to measure Paco_2 as a confirmatory diagnostic test. Therefore, serum bicarbonate can be used as a sensitive test to rule out hypercapnia, not to rule it in. An arterial blood gas demonstrating elevated Paco_2 with a normal pH confirms chronic alveolar hypoventilation. The subsequent evaluation to identify an etiology should initially focus on whether the patient has lung disease or chest wall abnormalities. Physical examination, imaging studies (chest x-ray and/or CT scan), and pulmonary function tests are sufficient to identify most lung/chest wall disorders leading to hypercapnia. If these evaluations are unrevealing, the clinician should screen for obesity hypoventilation syndrome (OHS), the most frequent sleep disorder leading to chronic hypoventilation, which is typically accompanied by obstructive sleep apnea (OSA). Several screening tools have been developed to identify patients at risk for OSA. The Berlin Questionnaire has been validated in a primary care setting and identifies patients likely to have OSA. The Epworth Sleepiness Scale (ESS) measures daytime sleepiness, with a score of 10 identifying individuals who warrant additional investigation; however, it is not a useful test to screen for sleep-disordered breathing. Owing to its ease of use, the STOP-Bang questionnaire has become a popular tool to screen for OSA and has been validated in various outpatient settings. The STOP-Bang survey has been used in preoperative anesthesia clinics to identify patients at risk of having OSA. In this population, it has 93% sensitivity and 90% negative predictive value. Additionally, the STOP-Bang questionnaire has been validated as a screening tool for OSA in sleep and surgical clinics. The probability of moderate and severe OSA steadily increases with higher STOP-Bang scores.

If the ventilatory apparatus (lung, airways, chest wall) is not responsible for chronic hypercapnia, then the focus should shift to respiratory drive and neuromuscular disorders. There is an attenuated increase in minute ventilation in response to elevated CO_2 and/or low O_2 in respiratory drive disorders. These diseases are difficult to diagnose and should be suspected when patients with hypercapnia are found to have normal respiratory muscle strength, normal pulmonary function, and normal alveolar-arterial Po_2 difference. Hypoventilation is more marked during sleep in patients with respiratory drive defects, and polysomnography often reveals central apneas, hypopneas, or hypoventilation. Brain imaging (CT scan or MRI) can sometimes identify structural abnormalities in the pons or medulla that result in hypoventilation. Chronic narcotic use or significant hypothyroidism can depress the central respiratory drive and lead to chronic hypercapnia as well.

Respiratory muscle weakness has to be profound before lung volumes are compromised and hypercapnia develops. Typically, physical examination reveals decreased strength in major muscle groups prior to the development of hypercapnia. Measurement of maximum inspiratory and expiratory pressures or forced vital capacity (FVC) can be used to monitor for respiratory muscle involvement in diseases with progressive muscle weakness. These patients also have increased risk for sleep-disordered breathing, including hypopneas, central and obstructive apneas, and hypoxemia. Nighttime oximetry and capnometry during polysomnography are helpful in better characterizing sleep disturbances in this patient population.

TREATMENT

Hypoventilation

Nocturnal noninvasive positive-pressure ventilation (NIPPV) has been used successfully in the treatment of hypoventilation and apneas, both central and obstructive, in patients with neuromuscular and chest wall disorders. Nocturnal NIPPV has been shown to improve daytime hypercapnia, prolong survival, and improve health-related quality of life when daytime hypercapnia is documented. ALS guidelines recommend consideration of nocturnal NIPPV if symptoms of hypoventilation exist and one of the

following criteria is present: Paco_2 >45 mmHg; nocturnal oximetry demonstrates oxygen saturation <88% for 5 consecutive min; maximal inspiratory pressure <60 cmH₂O; or sniff nasal pressure <40 cmH₂O and FVC <50% predicted. However, at present, there is inconclusive evidence to support preemptive nocturnal NIPPV use in all patients with neuromuscular and chest wall disorders who demonstrate nocturnal but not daytime hypercapnia. Nevertheless, at some point, the institution of full-time ventilatory support with either pressure or volume-preset modes is required in progressive neuromuscular disorders. There is less evidence to direct the timing of this decision, but ventilatory failure requiring mechanical ventilation and chest infections related to ineffective cough are frequent triggers for the institution of full-time ventilatory support.

Treatment of chronic hypoventilation from lung or neuromuscular diseases should be directed at the underlying disorder. Pharmacologic agents that stimulate respiration, such as medroxyprogesterone and acetazolamide, have been poorly studied in chronic hypoventilation and should not replace treatment of the underlying disease process. Regardless of the cause, excessive metabolic alkalosis should be corrected, as serum bicarbonate levels elevated out of proportion for the degree of chronic respiratory acidosis can result in additional hypoventilation. When indicated, administration of supplemental oxygen is effective in attenuating hypoxemia, polycythemia, and pulmonary hypertension. However, in some patients, supplemental oxygen, even at low concentrations, can worsen hypercapnia.

Phrenic nerve or diaphragm pacing is a potential therapy for patients with hypoventilation from high cervical spinal cord lesions or respiratory drive disorders. Prior to surgical implantation, patients should have nerve conduction studies to ensure normal bilateral phrenic nerve function. Small case series suggest that effective diaphragmatic pacing can improve quality of life in these patients.

HYPVENTILATION SYNDROMES

OBESITY HYPVENTILATION SYNDROME

The diagnosis of OHS requires the following: body mass index (BMI) >30 kg/m²; chronic daytime alveolar hypoventilation, defined as Paco_2 >45 mmHg at sea level in the absence of other known causes of hypercapnia; and evidence of sleep-disordered breathing. In almost 90% of cases, the sleep-disordered breathing is in the form of OSA, with close to 70% exhibiting severe OSA. Several international studies in different populations confirm that the overall prevalence of OSA syndrome, defined by an apnea-hypopnea index >5 and daytime sleepiness, is ~14% in men and 5% in women aged 30–70 years in the United States. Thus, the population at risk for the development of OHS continues to rise as the worldwide obesity epidemic persists. Although no population-based prevalence studies of OHS have been performed, some estimates suggest it may be as high as 0.4% of the U.S. adult population (or 1 in 263 adults).

Some, but not all, studies suggest that severe obesity (BMI >40 kg/m²) and severe OSA (AHI >30 events per h) are risk factors for the development of OHS. The pathogenesis of hypoventilation in these patients is the result of multiple physiologic variables and conditions including OSA, increased work of breathing, respiratory muscle impairment relative to the increased load because of excess adiposity, ventilation-perfusion mismatching, and depressed central ventilatory responsiveness to hypoxemia and hypercapnia. These defects in central respiratory drive often improve with treatment of sleep-disordered breathing with CPAP or NIPPV without any significant change in body weight, which suggests that decreased ventilatory responsiveness is a consequence rather than a primary cause of OHS. The treatment of OHS is similar to that for OSA: weight reduction and positive airway pressure therapy during sleep with either continuous positive airway pressure (CPAP) or NIPPV. There is evidence that substantial weight loss (i.e., 20–25% of actual body weight) alone normalizes Paco_2 in patients with OHS. Unfortunately, achieving and sustaining this

degree of weight loss without bariatric surgery are very challenging for most patients. Treatment with CPAP or NIPPV should not be delayed while the patient attempts to lose weight. CPAP improves daytime hypercapnia and hypoxemia in more than half of patients with OHS and concomitant severe OSA. Bilevel positive airway pressure without a backup rate (bilevel PAP spontaneous mode) should be reserved for patients not able to tolerate high levels of CPAP support or when obstructive respiratory events persist despite reaching the maximum CPAP pressure of 20 cmH₂O. NIPPV in the form of bilevel PAP with a backup rate (bilevel PAP ST or spontaneous timed) or volume-assured pressure support modes should be strongly considered if hypercapnia persists after several weeks of CPAP therapy with objectively proven adherence. Patients with OHS and no evidence of significant OSA are typically started on bilevel PAP ST or volume-assured pressure support modes, as are patients presenting with acute decompensated OHS. Finally, comorbid conditions that impair ventilation, such as COPD, should be aggressively treated in conjunction with coexisting OHS.

CENTRAL HYPOVENTILATION SYNDROME

This syndrome can present later in life or in the neonatal period, when it is often called Ondine's curse or congenital central hypoventilation syndrome (CCHS). Abnormalities in the gene encoding PHOX2b, a transcription factor with a role in neuronal development, have been implicated in the pathogenesis of CCHS. Regardless of the age of onset, these patients have absent respiratory response to hypoxia or hypercapnia, mildly elevated Paco₂ while awake, and markedly elevated Paco₂ during non-REM sleep. Interestingly, these patients are able to augment their ventilation and "normalize" Paco₂ during exercise and during REM sleep. These patients typically require NIPPV or mechanical ventilation as therapy and should be considered for phrenic nerve or diaphragmatic pacing at centers with experience performing these procedures.

HYPERVENTILATION

CLINICAL FEATURES

Hyperventilation is defined as ventilation in excess of metabolic requirements (CO₂ production) leading to a reduction in Paco₂. The physiology of patients with chronic hyperventilation is poorly understood, and there is no typical clinical presentation. Symptoms can include dyspnea, paresthesias, tetany, headache, dizziness, visual disturbances, and atypical chest pain. Because symptoms can be so diverse, patients with chronic hyperventilation present to a variety of health care providers, including internists, neurologists, psychologists, psychiatrists, and pulmonologists.

It is helpful to think of hyperventilation as having initiating and sustaining factors. Some investigators believe that an initial event leads to increased alveolar ventilation and a drop in Paco₂ to ~20 mmHg. The ensuing onset of chest pain, breathlessness, paresthesia, or altered consciousness can be alarming. The resultant increase in minute volume to relieve these acute symptoms only serves to exacerbate symptoms that are often misattributed by the patient and health care workers to cardiopulmonary disorders. An unrevealing evaluation for causes of these symptoms often results in patients being anxious and fearful of additional attacks. It is important to note that **anxiety disorders and panic attacks are not synonymous with hyperventilation**. Anxiety disorders can be both an initiating and sustaining factor in the pathogenesis of chronic hyperventilation, but these are not necessary for the development of chronic hypocapnia.

DIAGNOSIS

Respiratory symptoms associated with acute hyperventilation can be the initial manifestation of systemic illnesses such as diabetic ketoacidosis. Causes of acute hyperventilation need to be excluded before a diagnosis of chronic hyperventilation is considered. Arterial blood gas sampling that demonstrates a compensated respiratory alkalosis with a near normal pH, low Paco₂, and low calculated bicarbonate is necessary to confirm chronic hyperventilation. Other causes of respiratory alkalosis, such as mild asthma, need to be diagnosed and treated before

chronic hyperventilation can be considered. A high index of suspicion is required as increased minute ventilation can be difficult to detect on physical examination. Once chronic hyperventilation is established, a sustained 10% increase in alveolar ventilation is enough to perpetuate hypocapnia. This increase can be accomplished with subtle changes in the respiratory pattern, such as occasional sigh breaths or yawning 2–3 times per min.

TREATMENT

Hyperventilation

There are few well-controlled treatment studies of chronic hyperventilation owing to its diverse features and the lack of a universally accepted diagnostic process. Clinicians often spend considerable time identifying initiating factors, excluding alternative diagnoses, and discussing the patient's concerns and fears. In some patients, reassurance and frank discussion about hyperventilation can be liberating. Identifying and eliminating habits that perpetuate hypocapnia, such as frequent yawning or sigh breathing, can be helpful. Some evidence suggests that breathing exercises and dia-phragmatic retraining may be beneficial for some patients. The evidence for using medications to treat hyperventilation is scant. Beta blockers may be helpful in patients with sympathetically mediated symptoms such as palpitations and tremors.

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Sleep Apnea

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Obstructive sleep apnea (OSA) and central sleep apnea (CSA) are both classified as sleep-related breathing disorders. OSA and CSA share some risk factors and physiologic bases but also have unique features. Each disorder is associated with impaired ventilation during sleep and disruption of sleep, and each diagnosis requires careful elicitation of the patient's history, physical examination, and physiologic testing. OSA, the more common disorder, causes daytime sleepiness and impaired daily function. It is a cause of hypertension and is strongly associated with cardiovascular disease in adults and behavioral problems in children. CSA is less common and may occur alone or in combination with OSA. It can occur as a primary condition, as a response

to high altitude, or secondary to a medical condition (such as heart failure) or medication (such as opioids). Patients with CSA often report frequent awakenings and daytime fatigue and are at increased risk for heart failure and atrial fibrillation.

OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME

Definition OSA is defined on the basis of nocturnal and daytime symptoms as well as sleep study findings. Diagnosis requires the patient to have (1) either symptoms of nocturnal breathing disturbances (snoring, snorting, gasping, or breathing pauses during sleep) or daytime sleepiness or fatigue that occurs despite sufficient opportunity to sleep and is unexplained by other medical problems; and (2) five or more episodes of obstructive apnea or hypopnea per hour of sleep (the apnea-hypopnea index [AHI], calculated as the number of episodes divided by the number of hours of sleep) documented during a sleep study. OSA also may be diagnosed in the absence of symptoms if the AHI is ≥ 15 episodes/h. Each episode of apnea or hypopnea represents a reduction in breathing for at least 10 s and commonly results in a 3% drop in oxygen saturation or a brain cortical arousal. OSA severity can be characterized by the frequency of breathing disturbances (AHI), the amount of oxyhemoglobin desaturation with respiratory events, the duration of apneas and hypopneas, the degree of sleep fragmentation, and the level of reported daytime sleepiness or functional impairment.

Pathophysiology During inspiration, intraluminal pharyngeal pressure becomes increasingly negative, creating a “suctioning” force. Because the pharyngeal airway has no fixed bone or cartilage, airway patency is dependent on the stabilizing influence of the pharyngeal dilator muscles. Although these muscles are continuously activated during wakefulness, neuromuscular output declines with sleep onset. In patients with a collapsible airway, the reduction in neuromuscular output results in transient episodes of pharyngeal collapse (manifesting as an “apnea”) or near collapse (manifesting as a “hypopnea”). The episodes of collapse are typically terminated when ventilatory reflexes are activated and cause arousal, thus stimulating an increase in neuromuscular activity and opening of the airway. The airway may collapse at different sites, such as the soft palate (most common), tongue base, lateral pharyngeal walls, and/or epiglottis (Fig. 297-1). OSA may be most severe during rapid eye movement (REM) sleep, when neuromuscular output to the skeletal muscles is particularly low, and in the supine position due to gravitational forces.

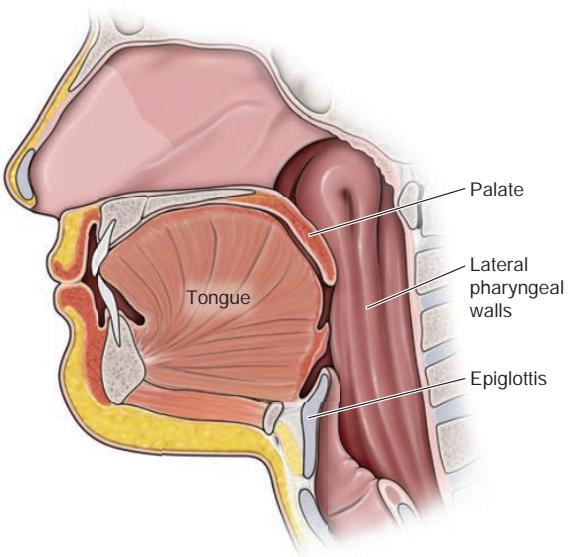


FIGURE 297-1 The structures causing airway collapse in obstructive sleep apnea include the palate, the tongue, and/or the epiglottis. In addition, collapse can also occur due to the lateral pharyngeal walls.

Individuals with a small pharyngeal lumen require relatively high levels of neuromuscular activation to maintain patency during wakefulness and thus are predisposed to airway collapse following the normal sleep-related reduction in pharyngeal muscle activity during sleep. The airway lumen may be narrowed by enlargement of soft tissue structures (tongue, palate, and uvula) due to fat deposition, increased lymphoid tissue, or genetic variation. Craniofacial factors such as mandibular retroposition or micrognathia, reflecting genetic variation or developmental influences, also can reduce lumen dimensions. In addition, lung volumes influence the caudal traction on the pharynx and consequently the stiffness of the pharyngeal wall. Accordingly, low lung volume in the recumbent position, which is particularly pronounced in the obese, contributes to collapse (less caudal traction). A high degree of nasal resistance (e.g., due to nasal septal deviation or polyps) can contribute to airway collapse by reducing intraluminal pressure downstream in the pharynx. High-level nasal resistance also may trigger mouth opening during sleep, which breaks the seal between the tongue and the palate and allows the tongue to fall posteriorly and occlude the airway.

Pharyngeal muscle activation is integrally linked to ventilatory drive. Thus, factors related to ventilatory control, particularly ventilatory sensitivity, arousal threshold, and neuromuscular responses to carbon dioxide (CO_2), contribute to the pathogenesis of OSA. A buildup in CO_2 during sleep activates both the diaphragm and the pharyngeal muscles. Pharyngeal activation stiffens the upper airway and can counteract inspiratory suction pressure and maintain airway patency to an extent that depends on the anatomic predisposition to collapse. However, pharyngeal collapse can occur when the ventilatory control system is overly sensitive to CO_2 , with resultant wide fluctuations in ventilation, ventilatory drive, and upper airway stiffness. Moreover, increasing levels of CO_2 during sleep result in central nervous system arousal, causing the individual to move from a deeper to a lighter level of sleep or to awaken. A low arousal threshold (i.e., awakening to a low level of CO_2 or ventilatory drive) can preempt the CO_2 -mediated process of pharyngeal muscle compensation and prevent airway stabilization. A high arousal threshold, conversely, may prevent appropriate termination of apneas, prolonging apnea duration and exacerbating oxyhemoglobin desaturation. Finally, any impairment in the ability of the muscles to compensate during sleep can contribute to collapse of the pharynx. The relative contributions of risk factors vary among individuals. Approaches to the measurement of these factors in clinical settings, with consequent enhancement of “personalized” therapeutic interventions, are being actively investigated.

Risk Factors and Prevalence The major risk factors for OSA are obesity, male sex, and older age. Additional risk factors include mandibular retrognathia and micrognathia, a positive family history of OSA, sedentary lifestyle, genetic syndromes that reduce upper airway patency (e.g., Down syndrome, Treacher-Collins syndrome), adenotonsillar hypertrophy (especially in children), menopause (in women), and various endocrine syndromes (e.g., acromegaly, hypothyroidism).

Approximately 40–60% of cases of OSA are attributable to excess weight. Obesity predisposes to OSA through the narrowing effects of upper airway fat on the pharyngeal lumen. Obesity also reduces chest wall compliance and decreases lung volumes, resulting in a loss of caudal traction on upper airway structures. Obese individuals are at a fourfold or greater risk for OSA than their normal-weight counterparts. A 10% weight gain is associated with a >30% increase in AHI. Even modest weight loss or weight gain can influence the risk and severity of OSA. However, the absence of obesity does not exclude this diagnosis.

The prevalence of OSA is twofold higher among men than among women. Factors that predispose men to OSA include android pattern of obesity (resulting in upper-airway and abdominal fat deposition) and relatively greater pharyngeal length, which increases collapsibility. Premenopausal women are relatively protected from OSA by the influence of sex hormones on ventilatory drive. The decline in sex difference in older age reflects an increased OSA prevalence in women after menopause. The pathogenesis and presentation of OSA also differ

2206 in men and women: compared to men, women have a lower arousal threshold and less neuromuscular collapsibility. Women tend to have shorter duration of apneas and apneas that occur predominantly in REM sleep. Failure to recognize these differences can contribute to underrecognition of OSA in women.

Variations in craniofacial morphology that reduce the size of the posterior airway space increase OSA risk. The contribution of skeletal structural features to OSA is most evident in nonobese patients. Identification of features such as retrognathia can influence therapeutic decision-making.

OSA has a strong genetic basis, as evidenced by its significant familial aggregation and heritability. For a first-degree relative of a patient with OSA, the odds of having OSA is approximately twofold higher than that of someone without an affected relative. Several genetic variants have been associated with prevalence of OSA or with related traits, such as the frequency of apneas and hypopneas, the duration of respiratory events, and degree of overnight levels of hypoxemia.

OSA prevalence varies with age, from 5 to 15% among middle-aged adults to >20% among elderly individuals, although in a majority of affected adults, the disorder is undiagnosed. There is a peak due to lymphoid hypertrophy among children between the ages of 3 and 8 years; with airway growth and lymphoid tissue regression during later childhood, prevalence declines. Then, as obesity prevalence increases in adolescence and adulthood, OSA prevalence again increases.

The prevalence of OSA is especially high among patients with certain medical conditions, including diabetes mellitus, hypertension, and atrial fibrillation. Individuals of East Asian ancestry appear to be at increased risk of OSA at relatively low levels of body mass index, reflecting the greater influence of craniofacial risk factors. In the United States, African Americans, especially children and young adults, are at higher risk for OSA than their white counterparts.

Course of the Disorder The precise onset of OSA is usually hard to identify. A person may snore for many years, often beginning in childhood, before OSA is identified. Weight gain may precipitate an increase in symptoms, which in turn may lead the patient to pursue an evaluation. OSA may become less severe with weight loss, particularly after bariatric surgery. In adults, there is a gradual increase in AHI with age, although marked increases and decreases in the AHI are uncommon unless accompanied by weight change.

APPROACH TO THE PATIENT

Obstructive Sleep Apnea/Hypopnea Syndrome

An evaluation for OSA should be considered in patients with symptoms of OSA and one or more risk factors. Screening also should be considered in patients who report symptoms consistent with OSA and who are at high risk for OSA-related morbidities, such as hypertension, diabetes mellitus, and cardiac and cerebrovascular diseases.

SYMPTOMS AND HISTORY

When possible, a sleep history should be obtained with assistance from a bed partner or household member. Snoring is the most common complaint; however, its absence does not exclude the diagnosis, as pharyngeal collapse may occur without tissue vibration. Gasping or snorting during sleep may also be reported, reflecting termination of individual apneas with abrupt airway opening. Dyspnea is unusual, and its absence generally distinguishes OSA from paroxysmal nocturnal dyspnea, nocturnal asthma, and acid reflux with laryngospasm. Patients also may describe frequent awakening or sleep disruption, which is more common among women and older adults. The most common daytime symptom is excessive daytime sleepiness, identified by a history of difficulty maintaining alertness or involuntary periods of dozing. However, many women preferentially report fatigue rather than sleepiness. Other symptoms include a dry mouth, nocturnal heartburn, diaphoresis of the chest and neck, nocturia, morning headaches, trouble concentrating,

irritability, and mood disturbances. Insomnia, which is common in the general population, may coexist with OSA. Although difficulty falling sleep is rarely caused by OSA, awakening at apnea termination may cause difficulty maintaining sleep, a symptom more likely to be reported by women than by men, and often responds to treatment of OSA. Several questionnaires that evaluate snoring frequency, self-reported apneas, and daytime sleepiness can facilitate OSA screening. The predictive ability of a questionnaire can be enhanced by a consideration of whether the patient is male or has risk factors such as obesity or hypertension.

PHYSICAL FINDINGS

Physical findings often reflect the etiologic factors for the disorder as well as comorbid conditions, particularly vascular disease. On examination, patients may exhibit hypertension and regional (central) obesity, as indicated by a large waist and neck circumference. The oropharynx may reveal a small orifice with crowding due to an enlarged tongue, a low-lying soft palate with a bulky uvula, large tonsils, a high-arched palate, or micro-/retrognathia. Since nasal resistance can increase the propensity to pharyngeal collapse, the nasal cavity should be inspected for polyps, septal deviation, allergic rhinitis, and other signs of obstruction. Because patients with heart failure are at increased risk for both OSA and CSA, a careful cardiac examination should be conducted to detect possible left- or right-sided cardiac dysfunction. Evidence of cor pulmonale suggests a comorbid cardiopulmonary condition; OSA alone is not thought to cause right-heart failure. A neurologic evaluation is needed to evaluate for conditions such as neuromuscular and cerebrovascular diseases, which increase OSA risk.

LABORATORY FINDINGS

Diagnostic Findings Since symptoms and signs do not accurately predict the severity of sleep-related breathing disturbances, specific diagnosis and categorization of OSA severity requires objective measurement of breathing during sleep. The gold standard for diagnosis of OSA is an overnight polysomnogram (PSG). A negative in-laboratory PSG usually rules out OSA. However, false-negative studies can result from night-to-night variation in OSA severity, particularly if there was insufficient REM sleep or less supine sleep during testing than is typical for the patient. Home sleep tests that record only respiratory and cardiac channels are commonly used as a cost-effective means for diagnosing OSA. However, a home study may yield a false-negative result if sleep time is not accurately estimated or in individuals experiencing hypopneas with arousals rather than oxyhemoglobin desaturation. Therefore, if there is a high prior probability of OSA, a negative home study should be followed by PSG.

The key physiologic information collected during a sleep study for OSA assessment includes measurement of breathing (changes in airflow, respiratory excursion), oxygenation (hemoglobin oxygen saturation), body position, and cardiac rhythm. In addition, PSGs and some home sleep studies measure sleep continuity and sleep stages (by electroencephalography, chin electromyography, electro-oculography, and actigraphy), leg movements, and snoring intensity. This information is used to quantify the frequency and subtypes of abnormal respiratory events during sleep as well as associated changes in oxygen hemoglobin saturation, arousals, and sleep stage distributions. **Tables 297-1** and **297-2** define the respiratory events scored and the severity guidelines employed during a sleep study. **Fig. 297-2** shows examples of sleep-related respiratory events. A typical sleep study report provides quantitative data such as the AHI (number of apneas plus hypopneas per hour of sleep) and the profile of oxygen saturation over the night (mean, nadir, time at low levels). Reports may also include the respiratory disturbance index, which includes the number of respiratory effort-related arousals in addition to the AHI. In-laboratory PSG also quantifies sleep latency (time from "lights off" to first sleep onset), the frequency of periodic limb movements during sleep, sleep

TABLE 297-1 Respiratory Event Definitions

- Apnea:** Cessation of airflow for 10 s during sleep, accompanied by:
 - Persistent respiratory effort (obstructive apneas, Fig. 297-2A), or
 - Absence of respiratory effort (central apneas, Fig. 297-2B)
- Hypopnea:** A 30% reduction in airflow for at least 10 s during sleep that is accompanied by either a 3% desaturation or an arousal (Fig. 297-2C)
- Respiratory effort-related arousal (RERA):** Partial obstruction that does not meet the criteria for hypopnea but provides evidence of increasing inspiratory effort (usually through pleural pressure monitoring) punctuated by an arousal (Fig. 297-2D)
- Flow-limited breath:** A partially obstructed breath, typically within a hypopnea or RERA, identified by a flattened or “scooped-out” inspiratory flow shape (Fig. 297-3)

TABLE 297-2 Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS): Quantification and Severity Scale

- Apnea-hypopnea index (AHI)^a:** Number of apneas plus hypopneas per hour of sleep
- Respiratory disturbance index (RDI):** Number of apneas plus hypopneas plus RERAs per hour of sleep
- Mild OSAHS:** AHI of 5–14 events/h
- Moderate OSAHS:** AHI of 15–29 events/h
- Severe OSAHS:** AHI of 30 events/h

^aEach level of AHI can be further quantified by level of sleepiness and associated hypoxemia.

Abbreviation: RERAs, respiratory effort-related arousals.

efficiency (percentage of time asleep relative to time in bed), arousal index (number of cortical arousals per hour of sleep), and time in each sleep stage. These metrics can further characterize the severity of OSA, which is associated with an increased arousal index, low sleep efficiency, and a reduction of time in deep (stage N3) and REM sleep and increase in light (stage N1) sleep. The detection of autonomic responses to apneas and hypopneas, such as surges in blood pressure, changes in heart rate, and abnormalities in cardiac rhythm, also provides relevant information on OSA severity.

Other Laboratory Findings Various imaging studies, including cephalometric radiography, upper airway MRI and CT, and fiberoptic endoscopy, can be used to identify anatomic risk factors for OSA. While these may be useful for planning surgical interventions, they are not indicated in the routine evaluation of OSA. Cardiac testing may yield evidence of impaired systolic or diastolic ventricular function or abnormal cardiac structure. Overnight blood pressure monitoring often displays a “nondipping” pattern (absence of the typical 10% fall of blood pressure during sleep compared to wakefulness). Arterial blood gas measurements made during wakefulness are usually normal. Waking hypoxemia or hypercarbia suggests coexisting cardiopulmonary disease or hypoventilation syndromes. Patients with severe nocturnal hypoxemia may have elevated hemoglobin values. A multiple sleep latency test or a maintenance of wakefulness test can be useful in quantifying sleepiness and helping to distinguish OSA from narcolepsy.

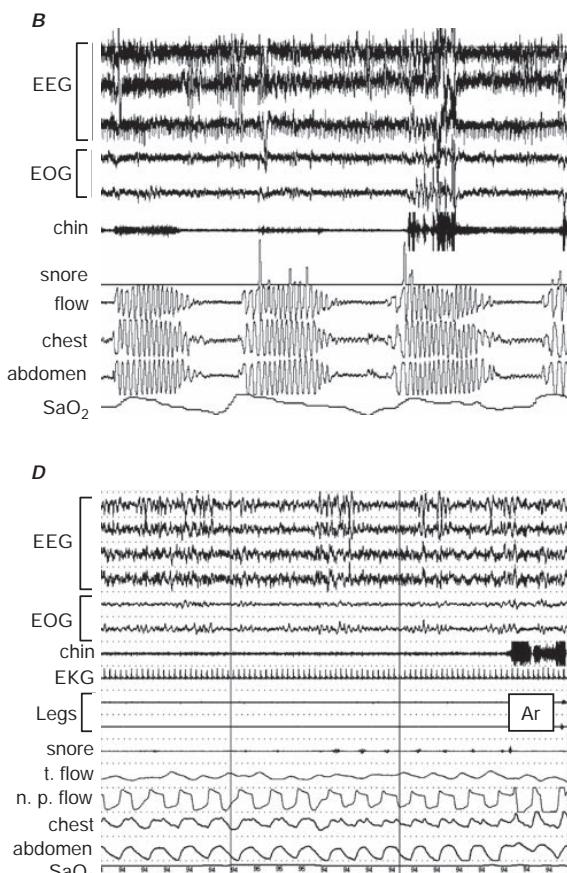
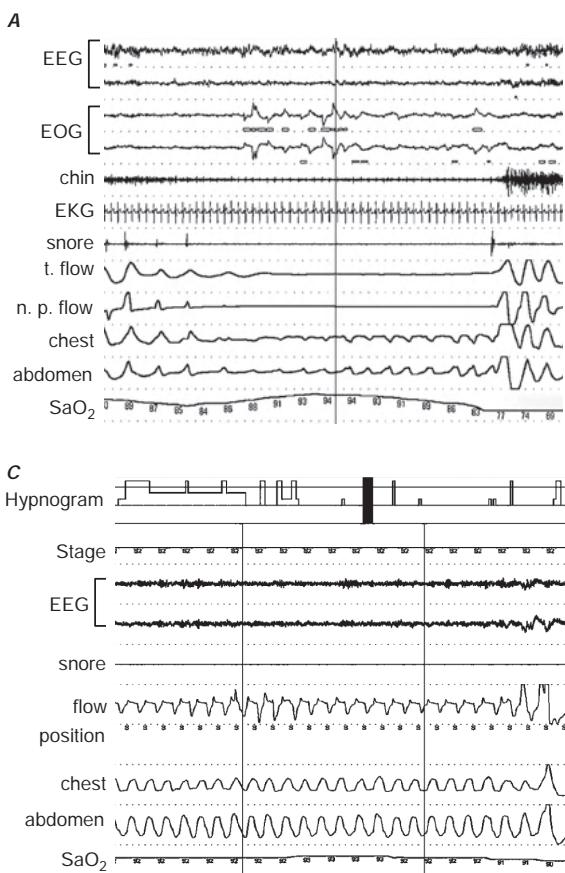


FIGURE 297-2 Obstructive apnea. **A.** There are 30 s of no airflow, as shown in the nasal pressure (n. p. flow) and thermistor-measured flow (t. flow). Note the presence of chest-abdomen paradox, indicating respiratory effort against an occluded airway. **B.** Central apnea in a patient with Cheyne-Stokes respiration due to congestive heart failure. The flat chest-abdomen tracings indicate the absence of inspiratory effort during the central apneas. **C.** Hypopnea. Partial obstruction of the pharyngeal airway can limit ventilation, leading to desaturation (a mild decrease in this patient, from 93 to 90%) and arousal. **D.** Respiratory effort-related arousal (RERA). Minimal flow reduction terminated by an arousal (Ar) without desaturation constitutes a RERA. EEG, electroencephalogram; EOG, electro-oculogram; EKG, electrocardiogram.

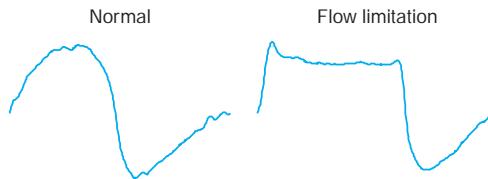


FIGURE 297-3 Example of flow limitation. The inspiratory flow pattern in a patient airway is rounded and peaks in the middle. In contrast, a partially obstructed airway exhibits an early peak followed by mid-inspiratory flattening, yielding a scooped-out appearance.

Health Consequences and Comorbidities OSA is the most common medical cause of daytime sleepiness and negatively influences quality of life. It is also strongly associated with cardiac, cerebrovascular, and metabolic disorders and with premature death. This broad range of health effects is attributable to the impact of sleep fragmentation, cortical arousal, and intermittent hypoxemia and hypercapnia on vascular, cardiac, metabolic, and neurologic functions. OSA-related respiratory events stimulate sympathetic overactivity, leading to acute blood pressure surges during sleep and nocturnal as well as daytime hypertension. OSA-related hypoxemia also stimulates release of acute-phase proteins and reactive oxygen species that exacerbate insulin resistance and lipolysis and cause an augmented prothrombotic and proinflammatory state. Inspiratory effort against an occluded airway causes large intrathoracic negative pressure swings, altering cardiac preload and afterload and resulting in cardiac remodeling and reduced cardiac function. Hypoxemia and sympathetic-parasympathetic imbalance also may cause electrical remodeling of the heart and myocyte injury.

HYPERTENSION OSA can raise blood pressure to prehypertensive and hypertensive ranges, increase the prevalence of a nondipping overnight blood pressure pattern, and increase the risk of uncontrolled and resistant hypertension. Elevations in blood pressure are due to augmented sympathetic nervous system activation as well as alterations in the renin-angiotensin-aldosterone system and fluid balance. Treatment of OSA with nocturnal continuous positive airway pressure (CPAP) has been shown to reduce 24-h ambulatory blood pressure. Although the overall impact of CPAP on blood pressure levels is relatively modest (averaging 2–4 mmHg), larger improvements are observed among patients who have a high AHI, report daytime sleepiness, or have resistant hypertension.

CARDIOVASCULAR, CEREBROVASCULAR, AND METABOLIC DISEASES Among the most serious health consequences of OSA may be its impact on cardiac and metabolic functions. Strong epidemiologic evidence indicates that OSA significantly increases the risk of coronary artery disease, heart failure with and without reduced ejection fraction, atrial and ventricular arrhythmias, atherosclerosis and coronary artery disease, stroke, and diabetes. Treatment of OSA has been shown to reduce several markers of cardiovascular risk and improve insulin resistance and, in uncontrolled studies, is associated with a decreased recurrence rate of atrial fibrillation. Recent randomized clinical trials, however, have failed to demonstrate that OSA treatment with CPAP reduces cardiac event rates or prolongs survival. These outcomes may reflect exclusion from these trials of patients with excessive sleepiness, as there is evidence that sleepy patients may have the greatest OSA-related cardiovascular risk. Limited adherence to treatment among trial participants or the widespread use of other effective secondary prevention measures, such as beta blockade, antiplatelet agents, and lipid-lowering therapy, may also limit the impact of CPAP on cardiovascular risk.

SLEEPINESS More than 50% of patients with moderate to severe OSA report daytime sleepiness. Patients with OSA symptoms have a twofold increased risk of occupational accidents. Individuals with elevated AHIs are involved in motor vehicle crashes approximately two to three times as often as persons with normal AHIs. Randomized controlled trials have shown that treatment of OSA with CPAP alleviates sleepiness as measured by either questionnaire or objective testing in

patients with both mild and more severe disease. However, the degree of improvement varies widely. Residual sleepiness may be due to several factors, including suboptimal treatment adherence, insufficient sleep time, other sleep disorders, or prior hypoxic-mediated damage in brain areas involved in alertness. Moreover, visceral adipose tissue, which is present in higher amounts in patients with OSA, releases somnogenic cytokines that may contribute to sleepiness. Thus, even after treatment, it is important to assess and monitor patients for residual sleepiness and to optimize treatment adherence, improve sleep patterns, and identify other disorders that may contribute to sleepiness. Careful and supervised use of alerting agents may be appropriate as adjunctive treatment in patients in whom sleepiness does not respond to CPAP alone.

QUALITY OF LIFE AND MOOD Reductions in health-related quality of life are common in patients with OSA, with the largest decrements observed in scales that measure physical functioning and energy levels. Work-related productivity also has been shown to improve in patients with moderate to severe OSA treated with CPAP. Numerous studies, including a large-scale trial of minimally symptomatic patients, have shown that treatment with CPAP can improve these patient-reported outcomes. Depressive symptoms, in particular somatic symptoms (irritability, fatigue, lack of energy), are commonly reported in OSA and improve with CPAP.

TREATMENT

Obstructive Sleep Apnea

A comprehensive approach to the management of OSA is needed to reduce risk factors and comorbidities. The clinician should seek to identify and address lifestyle and behavioral factors as well as comorbidities that may be exacerbating OSA. As appropriate, treatment should aim to reduce weight; optimize sleep duration (7–9 h); regulate sleep schedules (with similar bedtimes and wake times across the week); encourage the patient to avoid sleeping in the supine position; treat nasal allergies; increase physical activity; eliminate alcohol ingestion (which impairs pharyngeal muscle activity) within 3 h of bedtime; and minimize use of opiate medications. Sedative hypnotic medications have inconsistent effects on OSA but should be avoided in most patients with moderate to severe OSA. Patients should be counseled to avoid drowsy driving.

CPAP is the standard medical therapy with the highest level of evidence for efficacy. Delivered through a nasal or nasal-oral mask, CPAP works as a mechanical splint to hold the airway open, thus maintaining airway patency during sleep. An overnight CPAP titration study can determine the optimal pressure setting that reduces the number of apneas/hypopneas during sleep, improves gas exchange, and reduces arousals; however, the use of “auto-titrating” CPAP devices used in home settings has eliminated the need for titration sleep studies in many patients. Rates of adherence to CPAP treatment are highly variable (average, 50–80%) and may be improved with support by a skilled health care team who can address side effects, help the patient “problem solve,” and provide motivational education (**Table 297-3**). Despite the limitations of

TABLE 297-3 Side Effects of Continuous Positive Airway Pressure (CPAP) and Their Treatments

SIDE EFFECT	TREATMENT
Nasal congestion	Provide heated humidification, administer saline/steroid nasal sprays
Claustrophobia	Change mask interface (e.g., to nasal prongs), promote habituation (i.e., practice breathing on CPAP while awake)
Difficulty exhaling	Temporarily reduce pressure, provide bilevel positive airway pressure
Bruised nasal ridge	Change mask interface, provide protective padding
Aerophagia	Administer antacids

CPAP, controlled studies have demonstrated its beneficial effect on alertness, mood, quality of life, work-related productivity, blood pressure, and insulin sensitivity. Uncontrolled studies also indicate a favorable effect on cardiovascular outcomes, cardiac ejection fraction, atrial fibrillation recurrence, and mortality risk.

Oral appliances for OSA work by advancing the mandible, thus opening the airway by repositioning the lower jaw and pulling the tongue forward. These devices generally work better when customized for patient use; maximal adaptation can take several weeks. Efficacy studies show that these devices can reduce the AHI by 50% in two-thirds of individuals, although these data are based largely on patients with mild OSA. Some patients with moderate or severe OSA respond to oral appliances as well, although no consistent predictors of success have been identified in these groups, and thus, follow-up sleep testing is recommended. Side effects of oral appliances include temporomandibular joint pain and tooth movement; thus, they require that the patient have adequate dental and periodontal structures. Oral appliances are most often used for treating patients with mild/moderate OSA or patients who do not tolerate CPAP. However, as some patients are more adherent to oral appliances than to CPAP, these devices are under investigation for treatment of more severe disease.

Upper airway surgery for OSA is less efficacious than CPAP and is mostly reserved for the treatment of patients who snore, have mild OSA, or cannot tolerate CPAP. Uvulopalatopharyngoplasty (removal of the uvula and the margin of the soft palate) is the most commonly performed surgery for OSA and, although results vary greatly, is generally less successful than treatment with oral appliances. Upper airway surgery is less effective in severe OSA and in obese patients. Success rates may be higher for multilevel surgery (involving more than one site/structure) performed by an experienced surgeon, but the selection of patients is an important factor and relies on careful targeting of culprit areas for surgical resection. Bariatric surgery is an option for obese patients with OSA and can improve not only OSA but also other obesity-associated health conditions. Other procedures that can decrease snoring but have minimal effects on OSA include injection of a hardening agent to the soft palate (resulting in stiffening), radiofrequency ablation, laser-assisted uvulopalatoplasty, and palatal implants.

Upper airway neurostimulation is a recently tested alternative treatment for OSA. Unilateral stimulation of the hypoglossal nerve through a surgically implanted device was shown to significantly decrease the AHI and improve a number of patient-reported outcomes, such as sleepiness and quality of life, for a duration of at least 5 years after treatment in carefully selected patients. This therapy is reserved for patients who cannot tolerate or fail CPAP therapy. Current inclusion criteria are moderate to severe OSA (AHI 15–65), BMI <32 kg/m², and absence of complete concentric collapse at the level of the velum documented by awake and drug-induced endoscopy (a predictor of response to surgery). Additional research is underway to further evaluate longer-term effectiveness and potential utility of this treatment in other patient groups.

Supplemental oxygen can improve oxygen saturation, but there is little evidence that it improves OSA symptoms or the AHI in unselected patients. There is conflicting evidence regarding the effect of supplemental oxygen on blood pressure in patients with OSA.

CENTRAL SLEEP APNEA

CSA, which is less common than OSA, may occur in isolation or, more often, in combination with obstructive events in the form of “mixed” apneas. CSA is often caused by an increased sensitivity to PCO_2 , which leads to an unstable breathing pattern that manifests as hyperventilation alternating with apnea. A prolonged circulation delay between the pulmonary capillaries and carotid chemoreceptors is also a contributing cause; thus, individuals with congestive heart failure are at risk for CSA. With prolonged circulation delay, there is a crescendo-decrescendo breathing pattern known as *Cheyne-Stokes breathing* (Fig. 297-2B). Other risk factors for CSA include opioid medications (which appear to have a dose-dependent

effect on CSA) and hypoxia (e.g., breathing at high altitude). In some individuals, CPAP—particularly at high pressures—seems to induce central apnea; this condition is referred to as *complex sleep apnea* or *treatment-emergent central sleep apnea*. Rarely, CSA may be caused by blunted chemosensitivity due to congenital disorders (congenital central hypoventilation syndrome) or acquired factors. CSA is an independent risk factor for the development of both heart failure and atrial fibrillation, possibly related to elevations in sympathetic nervous system activity that accompany this disorder; alternatively, CSA may be an early marker of subclinical myocardial dysfunction. Patients with CSA may report symptoms of frequent awakenings as well as daytime fatigue. Treatment of CSA is difficult and depends on the underlying cause. Limited data suggest that supplemental oxygen can reduce the frequency of central apneas, particularly in patients with hypoxemia, and ongoing clinical trials are further evaluating supplemental oxygen for use in patients with heart failure and CSA. Cheyne-Stokes breathing is treated by optimizing therapy for heart failure. At this time, there is no good evidence that CPAP, including *adaptive servoventilation* (a form of ventilatory support that attempts to regularize the breathing pattern), improves health outcomes in patients with Cheyne-Stokes breathing without OSA, and in fact, it may be detrimental in those with heart failure associated with reduced ejection fraction.

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298 Lung Transplantation

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END-STAGE LUNG DISEASE AND INDICATIONS FOR LUNG TRANSPLANTATION

For the purpose of lung allocation score (LAS) prioritization for organ allocation, the United Network for Organ Sharing (UNOS) divides advanced lung disease diagnoses into four categories: (A) obstructive lung disease (including non-cystic fibrosis-related bronchiectasis and obliterative bronchiolitis), (B) pulmonary vascular disease, (C) cystic fibrosis, and (D) restrictive lung disease. Historically, obstructive lung disease was the most common indication for transplantation, but since the implementation of the LAS system, idiopathic pulmonary fibrosis (IPF), the most common restrictive lung disease, has become an increasingly frequent indication for transplantation. Prior to the era of antifibrotic therapy, the average life expectancy from the time of diagnosis of IPF was 3–5 years, making patients with this disease the cohort to experience most clearly a survival benefit from lung transplantation. As a result, the LAS system prioritizes patients with IPF. Similarly, patients who experience secondary effects of their lung disease, including pulmonary hypertension, right heart dysfunction, and hypercarbia, are prioritized for allocation and should be considered for referral for transplant evaluation irrespective of other markers of disease severity.

Generally, the trajectory of decline and evolution of disease are key indicators of the appropriate timing for referral and listing for lung transplantation, rather than absolute thresholds of disease severity. However, suggested guidelines for referral have been elucidated for specific disease states. For example, in chronic obstructive pulmonary disease, the most common obstructive lung disease for which transplantation is considered, the Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Index is often used as a marker of disease severity, with an index of 5 an appropriate indication for referral for evaluation, and 7 for listing for transplantation. Other suggested markers for transplant consideration in obstructive lung disease include pulmonary function test (PFT) data, such as a forced expiratory volume in 1 s of <25% predicted. The frequency and severity of exacerbations of disease should also be considered in determining the appropriate timing of referral.

With the marked advances in medical therapy for pulmonary vascular disease over the past decade, transplantation for pulmonary vascular disease has become less frequent but is still an important consideration for patients who progress despite, or are refractory to, treatment. Functional assessments such as New York Heart Association class III or IV limitations and hemodynamic measurements such as cardiac index <2 L/min per m² would suggest consideration for evaluation and listing. Patients with diagnoses generally poorly responsive to therapy such as pulmonary veno-occlusive disease should be referred early for evaluation.

Patients with cystic fibrosis (CF) have historically been considered for evaluation when the FEV1 reaches approximately 30% predicted. However, with the exciting development of therapies targeting the CF transmembrane receptor, providers should keep in mind the potential for improvement in pulmonary function after treatment initiation. Despite this potential for pharmacotherapeutic response, referral and completion of testing should be considered so that patients are prepared for listing should they fail to see improvement or experience worsening of disease on therapy. Moreover, patients who experience acceleration of acute exacerbation rate, recurrent hemoptysis, worsening functional and/or nutritional status, or colonization with resistant bacteria should also be assessed for transplantation irrespective of pulmonary function results.

Despite treatment progress with the development of antifibrotic therapy for IPF and other progressive fibrosing interstitial lung diseases, these therapies do not reverse the disease but only slow the rate of lung function decline. Therefore, transplant referral for patients with IPF and other fibrosing lung diseases should still be considered at the time of diagnosis. Forced vital capacity <80% predicted or diffusing capacity for carbon monoxide <40% predicted, failure to respond to medical therapy, decline in pulmonary function tests on therapy, and functional decline are additional indications for transplant consideration in patients with other restrictive lung diseases.

CONTRAINDICATIONS TO LUNG TRANSPLANTATION

Absolute Contraindications As experience with lung transplantation increases, and as lung allocation policy prioritizes patients with higher acuity of disease and with diseases affecting older age groups, recipient selection criteria have become more liberal compared to prior eras. While published guidelines suggest absolute and relative contraindications to transplantation, these criteria are in constant evolution, and each program ultimately establishes its own selection algorithms based upon clinical expertise, experience, program size and resources, and referral patterns.

Examples of absolute contraindications to lung transplantation (**Table 298-1**) include anatomic and technical considerations that would affect the ability to complete the transplant procedure, such as chest wall or spinal deformities or malacia of the large airways. Surgical input is critical in making such determinations. In addition, untreatable and/or irreversible organ dysfunction may preclude isolated lung transplantation. Cirrhosis of the liver, uncorrectable disease of the coronary arteries not amenable to combined surgical intervention

TABLE 298-1 Contraindications to Lung Transplantation

	ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
Surgical considerations	Anatomic abnormalities not amenable to transplant procedure	
Age		>65 years
Functional status	Immobility, inability to participate in physical therapy/rehabilitation	Limited functional status as defined by 6-minute walk distance
Medical comorbidities	Untreatable, irreversible organ dysfunction Active malignancy or malignancy with insufficient remission period Active bacterial bloodstream infection Uncontrolled viral infection (HIV, hepatitis)	Chronic kidney disease Infection resistant to treatment or of high risk for posttransplant morbidity/mortality (<i>Burkholderia cenocepacia</i> , <i>Mycobacterium abscessus</i>)
Nutritional		BMI <18 or >30–35
Psychosocial	Untreatable, irreversible psychiatric disorder with potential to impact transplant outcome Active substance abuse Other circumstances that would impede ability to participate in and comply with posttransplant care	Limited social supports History of noncompliance with medical treatment

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus.

during the transplant procedure, or other forms of uncorrectable atherosclerotic or vascular disease may make transplantation too high risk for consideration. Renal dysfunction is of particular concern given the known nephrotoxicity of calcineurin inhibitors, which are the mainstay of posttransplant immune suppression.

Relative Contraindications Age in and of itself is typically not a contraindication to transplantation at most centers. However, older patients with significant medical comorbidities may be at prohibitive risk for transplantation, and functional status and frailty may worsen in this setting. Published analyses of the Scientific Registry of Transplant Recipients, a comprehensive database of transplant outcomes, have consistently shown that functional capacity, as assessed by 6-minute walk distance, is inversely correlated with both wait list and posttransplant mortality. As a result, most programs utilize some assessment of functional status as a criterion for transplant candidacy.

Frailty, independent of walk distance, has also been recognized increasingly as a marker of poor outcome after lung transplantation, and can be assessed using a number of instruments, including the Short Physical Performance Battery (SPPB), Fried Frailty Phenotype (FFP), and others. Most studies utilizing these instruments have been conducted at single centers. While both SPPB and FFP have been shown to correlate with the LAS, FFP has a stronger correlation, and SPPB and FFP may not correlate with each other. Further study is needed to determine prospectively the relationship between these measures assessed in the pretransplant setting and posttransplant outcomes.

Patients with a history of malignancy are generally required to have experienced a period of remission prior to consideration for transplantation. The necessary length of disease-free survival should be determined in the context of the type of malignancy, stage at diagnosis, and likelihood of recurrence, and often varies by program.

A history of respiratory infection and colonization with resistant organisms is of particular concern in the CF and bronchiectasis populations, although it could affect patients with any advanced lung

disease and a history of respiratory infection. Data on outcomes in the presence of resistant *Pseudomonas aeruginosa* infection are conflicting, but in general, patients who have demonstrated a response to an antimicrobial regimen, even if colonized with resistant organisms, can be considered for transplantation. *Burkholderia cepacia* complex, another group of gram-negative organisms that can infect patients with CF, also presents a unique concern for transplantation. Data show that *B. cenocepacia* (formerly known as Genomovar III) portends the highest risk posttransplant, often leading to bacteremia, abscess formation, and early mortality. *B. dolosa* and *gladioli* may cause similar posttransplant complications. Patients colonized with other *Burkholderia* species appear to have posttransplant outcomes comparable with the noncolonized population, and, therefore, can be considered for transplantation. Published guidelines suggest that those programs offering transplantation to patients colonized with *B. cenocepacia* do so under a research structure and after a specific discussion of the risks of transplantation in this setting with the patients. Other infectious considerations in lung transplant candidates include mycobacterial infections, particularly with rapidly growing organisms such as *M. abscessus*, which can lead to chronic, refractory infections and infections of the chest wall. In the case of fungal infection, assessment of the pathogenicity of the organism, resistance patterns, and, in some cases, responsiveness to pretransplant treatment, is beneficial in determining the safety of transplantation.

A history of viral infections such as hepatitis and human immunodeficiency virus (HIV) is generally not considered a contraindication to transplantation. Demonstration of adequate control of infection and responsiveness to therapy are important in preparation for transplantation, and development of a treatment plan that minimizes toxicity and drug interactions, in consultation with transplant pharmacy, should be completed prior to placement on the wait list. Collaborative assessment with transplant infectious disease experts is beneficial whenever the infectious history is a concern for transplant safety.

Nutritional status is another important element to assess in determining candidacy for lung transplantation. Nutritional status has been shown to have a U-shaped relationship with transplant outcomes, with increased mortality risk associated with both underweight (BMI <18) and obesity (specifically BMI >35). Consultation with nutritional experts may allow for modification of this risk prior to transplant. In some underweight patients, placement of an enteral feeding tube and initiation of enteral feedings may be considered.

Psychosocial assessment is also a key component of the evaluation of patients under consideration for lung transplantation, and a multidisciplinary approach with transplant social work, psychiatry, and financial care coordination is often helpful. Assessment for and optimization of psychiatric disorders such as anxiety and depression, which can be exacerbated in the setting of transplantation, substance abuse disorders, and compliance with medical therapy recommendations are all important parts of the pretransplant evaluation. Perioperative pain management planning in the setting of medical therapy for opioid use disorder may require additional multidisciplinary input, but the need for this management plan alone should not preclude transplantation. Transplant candidates require a strong support system given their potential posttransplant care needs. Additionally, confirmation of insurance coverage for all phases of transplant care, expected medication copayments, and financial resources to support other expenses in the setting of transplantation should be completed during the transplant evaluation. Fundraising opportunities and subsidies for medications may need to be pursued in order to proceed safely with listing.

LUNG TRANSPLANT CANDIDATE MANAGEMENT

Lung transplant candidates need meticulous and exquisite medical care to ensure that they are in excellent condition at the time of transplant. Oxygen is prescribed to maintain adequate systemic oxygenation to allow for moderate physical activity and exertion. Patients should be enrolled in pulmonary rehabilitation programs, if available, and should continue to participate in daily physical exercises. Fluid management is important to consider and restriction of free water and salt intake is recommended.

Patients with pulmonary vascular disease and severe pulmonary hypertension awaiting lung transplantation need special attention to maintain adequate right ventricular function. The use of pulmonary vasodilator therapy is recommended and should not be stopped prior to transplant. Patients who develop secondary pulmonary hypertension should also be assessed for the utility of direct pulmonary vasodilator therapy. Periodic assessment of right ventricular function with echocardiography is recommended, and in patients with clearly worsening ventricular function, right heart catheterization and assessment for responsiveness to short-acting vasodilator therapy should be considered.

In restrictive lung disease patients awaiting transplant, consideration should be given to continuation of immune modulators and/or antifibrotic therapy. Studies are ongoing to determine the impact of antifibrotic therapy on posttransplant wound healing. Additionally, increased pulmonary vascular resistance can occur in these patients as the disease progresses, and acute exacerbations have been shown to be associated with severe acute decrease in right ventricular function. Steroids have been utilized in the management of acute exacerbations; however, the negative sequelae of chronic steroid use on wound healing is well established. Therefore, steroid use should be limited as much as possible, and if unavoidable, should be tapered rapidly.

Patients with CF can have pancreatic dysfunction leading to difficulty in maintaining normal blood glucose levels; uncontrolled diabetes mellitus can make the management of posttransplant blood glucose very challenging. Therefore, optimization of diabetes management should be pursued prior to transplantation.

Despite optimal medical therapy, the underlying disease in wait-listed patients will almost always continue to worsen. Prioritization of patients awaiting lung transplant is determined by the LAS. The score is generated by giving weight to risk factors associated with predicted mortality while on the wait list while also accounting for the expected posttransplant survival of the patient. This composite score is then normalized to generate a score between 0 and 100. The higher the score, the more prioritized the patient, and the higher the probability of a suitable donor match for the recipient. The main factors that influence the LAS are the underlying diagnosis of the patient (such as restrictive lung disease, as mentioned above), the demographics of the patient (gender and age), and the patient's current clinical status. The more acutely ill the patient (the patient's oxygen requirements, pulmonary hypertension, use of invasive support systems such as mechanical circulatory support or ventilatory support, limited mobility, lack of independence with activities of daily living), the higher the score. This results in a system of organ allocation that is most efficient at ensuring that the sickest patients receive the organs available. However, despite this prioritization strategy, patients continue to expire at a rate of 10–12 patient deaths per 100 patient-years on the wait list. It is critical for the best outcomes in these patients that ongoing clinical assessment and frequent updates of the LAS are routine aspects of their management.

A major consequence of improved efficiency in matching the sickest patients to the available pool of donors has been an increased use of extracorporeal membrane oxygenation (ECMO) devices to bridge the most critically ill patients to transplant. Mechanical circulatory support with ECMO allows for patients to be potentially weaned from the ventilator, to maintain physical activity and ambulation, and to be in a state of greater robustness as they await transplant. The posttransplant survival rate of patients bridged to transplant with ECMO is lower than patients transplanted without the need for ECMO but better than patients who had previously been transplanted directly from mechanical ventilatory support. Furthermore, with improvements in membrane oxygenator technology, platform miniaturization, and improvements in cannula design, outcomes continue to improve.

DONOR CONSIDERATIONS

The ideal lung donor has remained constant since the inception of lung transplantation in the 1980s (Table 298-2). A donor between 25–40 years of age, with a $\text{PaO}_2/\text{FiO}_2$ ratio >350, no smoking history, a clear chest x-ray, clean bronchoscopy, and minimal ischemic time is considered the ideal donor; however, it is quite rare that a donor

TABLE 298-2 Characteristics of the Ideal Lung Donor

Donor age	<55 years
ABO compatibility	Identical
Chest radiograph	Clear
PaO ₂ :FiO ₂	>300 on PEEP 5-cm H ₂ O
Tobacco history	<20 pack-years
Chest trauma	Absent
Evidence of aspiration	Absent
Prior thoracic surgery	None
Sputum gram stain	Negative
Bronchoscopy findings	No purulent secretions

meets all of these criteria for transplantation. In fact, the vast majority of donor lungs used for transplant fall outside these ideal lung donor criteria as established more than three decades ago. Donors must have irreversible brain injury, and the majority of donors are brain dead. Only 20% of all donors with brain death are suitable lung donors due to the development of severe neurogenic pulmonary edema and increased susceptibility of potential lung allografts to infection and injury.

Absolute contraindications to lung donation include radiographic evidence of chronic lung disease such as emphysema and pulmonary fibrosis. Other absolute contraindications include active malignancy, a donor history of severe asthma requiring multiple hospitalizations, and positive HIV status. Relative contraindications include older donor age, severe thoracic trauma with extensive pulmonary contusions, the presence of pulmonary hypertension, and prolonged donor hypotension or acute hypoxemia.

The standard lung donor evaluation includes a donor medical and social history, physical examination, and laboratory examination. Chest imaging is mandatory, as are arterial blood gases, bronchoscopy, and serological tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C, HIV, toxoplasma, rapid plasma reagent, and herpes simplex virus. The presence of consolidation and atelectasis, while not absolute contraindications to transplant, are often difficult to assess with noncontrast radiographic imaging alone. Ventilation parameters must be evaluated to ensure adequate compliance of the donor lungs, with peak airway pressures <30 cmH₂O being ideal. Direct on-site inspection of the lungs and assessment for nodules, compliance, and full expansion are the final necessary steps before acceptance of donor lungs for transplant.

More recently, there has been an expanded use of allografts from donors after cardiac death (DCD) due to the ability to rehabilitate donor lungs using ex vivo lung perfusion (EVLP). DCD donors are patients who present with irreversible brain injury but without overt brain death. The potential donor allografts are often exposed to a period of prolonged warm ischemia during the donation process; there has been a concern about early graft dysfunction after DCD donation. Steen and colleagues in Lund demonstrated that EVLP could be used to assess these marginal donors prior to transplant. The landmark publication of the Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation trial in 2011 generated renewed interest in DCD lung donors. The group from the University of Toronto was also able to demonstrate that brain-dead donors with unacceptable donor lung parameters could be rehabilitated with the use of EVLP. They were able to salvage up to 50% of selected unsuitable donor lung allografts with the use of acellular normothermic hyperosmotic perfusion with excellent short-term outcomes.

Donor Management Brain death causes severe perturbations in the potential donor lung allograft function. The development of severe pulmonary edema often accompanies brain death. The hemodynamic instability and neurogenic shock that can accompany brain death are also major stressors on the preservation of donor allograft function. The primary goal of donor management is, therefore, the maintenance of hemodynamic stability and preservation of donor lung function. Judicious fluid resuscitation and avoidance of excessive resuscitation

should be employed. Volume replenishment should be limited to maintain the central venous pressure between 5 and 8 mmHg. In general, crystalloid fluid boluses are to be avoided. Diabetes insipidus is common in donors and requires the use of intravenous vasopressin to prevent excessive urine loss. In general, blood transfusions should be avoided; however, if necessary, CMV-negative and leukocyte-filtered blood should be used whenever possible. Hypothermia should be avoided as it predisposes to ventricular arrhythmias and metabolic acidosis.

Excessive oxygen delivery should be minimized to prevent free-radical injury to the potential lung allograft. Positive end-expiratory pressures on the ventilator should be maintained to avoid the development of atelectasis. More recently, airway pressure release ventilation modes of ventilation have been utilized to preserve lung function and minimize barotrauma from prolonged ventilation.

PROCUREMENT OPERATION

Prior to incision, a thorough bronchoscopic evaluation is completed. The anatomy of the donor airways is defined. Any secretions that may be present are evacuated and the airways are examined to rule out the presence of any lesions or masses. The epithelial lining is inspected for evidence of excessive friability and hemorrhage, which may indicate significant infection. A median sternotomy incision is employed to access the chest for lung procurement. The pleural spaces are opened and both lungs are inspected, palpated, and gently recruited to evaluate for suspicious nodules, consolidation, and/or pulmonary infarction.

The donor is systemically heparinized, and the main pulmonary artery is cannulated. Fifteen minutes prior to initiation of the explant, prostacyclin is introduced into the main pulmonary artery and allowed to circulate through the lungs. This vasoreactive prostanoid helps to ensure adequate pulmonary flush by dilating the pulmonary vasculature. The heart is arrested first, then the pulmonoplegia solution is instilled into the lungs at a low controlled pressure. Topical iced-saline solution is instilled into both pleural spaces. After the heart has been explanted, the individual pulmonary veins are flushed retrogradely. The lungs are then re-expanded, the trachea is clamped, and the explanted allograft is stored in ice-cold saline solution for transport. If the right and left lungs are being procured for different recipients, the posterior left atrium, the main pulmonary artery, and the left main-stem bronchus are divided to separate the right and left lungs, and the organs are stored and shipped separately.

RECIPIENT OPERATION AND EARLY POSTTRANSPLANT CONSIDERATIONS

Recipient Operation The recipient operation can be divided into two parts. The first part involves the explant of the native lung and the second part involves the implant of the new lung. There are generally three main surgical approaches to the completion of the operation: a right or left thoracotomy, a transverse thoracosternotomy (clamshell), or median sternotomy. These approaches are all favored by various centers for different benefits. The thoracotomy approach allows for explant and implant of donor lungs without the use of cardiopulmonary bypass (CPB) and is often the preferred approach for single-lung transplant. The clamshell incision offers the advantages of increased exposure compared to either thoracotomy or median sternotomy but comes at the cost of greater morbidity and postoperative wound complications. This incision can be used to perform bilateral lung transplants and allows for the possibility of avoiding CPB. A median sternotomy approach can be used to perform bilateral lung transplant. This approach offers the advantage of fewer wound complications, less postoperative pain, and flexibility with more complex or concomitant cardiac procedures at the time of lung transplant. This approach mandates the use of CPB. The routine use of CPB allows for early pneumonectomies without hemodynamic compromise and can significantly reduce the ischemic time to the second allograft. Additionally, overcirculation to the first allograft can be minimized with the routine use of CPB. Others prefer to avoid CPB as avoidance may be associated

with decreased need for blood product administration and lower incidence of primary graft dysfunction.

Anesthetic monitoring for lung transplant should include arterial pressure monitoring, pulse oximetry, continuous electrocardiographic monitoring, temperature monitoring, and urine output monitoring. Large-bore IV access and central venous access are vital to manage the patient safely. On a selective basis, pulmonary artery pressure monitoring and transesophageal echocardiographic monitoring may be useful. For patients without the planned use of CPB, double-lumen endotracheal tubes are mandatory, whereas they can be avoided for patients transplanted on CPB.

Once access to the thorax has been completed, the hilar structures are isolated and divided. The bronchial anastomosis is completed first, and the anastomosis is checked to ensure that it is secure by insufflating the lung gently while keeping the anastomosis under saline solution to observe for bubbles. The donor left atrial cuff incorporating the pulmonary vein is connected to the native left atrium and the donor right or left pulmonary artery is connected to the native pulmonary artery. After completion of the vascular anastomoses, the lungs are gently reperfused. During this early reperfusion period, lung-protective ventilation strategies are employed and oxygen tension is reduced. The patient is transitioned to normal ventilation, drains are placed in the thoracic cavity, and the wounds are closed.

Induction of Immunosuppression Initiation of immunosuppression starts with induction of the patient under general anesthesia. Many programs utilize an induction agent (most commonly an IL-2 receptor/CD25 antagonist, but antithymocyte globulin, anti-CD52 monoclonal antibodies, or other induction agents may also be used), and systemic corticosteroids and purine modulators are administered after induction is complete. If an IL2 receptor antagonist is utilized for induction, a second dose is administered 4 days after the original dose. An additional dose of methylprednisolone is administered after allograft reperfusion in the operating room. Three-drug immune suppression is initiated with a calcineurin inhibitor, purine modulator, and continued systemic corticosteroids. In patients with severe acute renal dysfunction, calcineurin inhibitor initiation may be delayed.

Perioperative Considerations and Complications Early morbidity and mortality after lung transplant most commonly are sequelae of primary graft dysfunction or infection. Very rarely, hyperacute rejection has been observed; however, with the implementation of robust systems to ensure ABO and HLA compatibility at the time of transplant, the occurrence of hyperacute rejection is extremely uncommon. Primary graft dysfunction (PGD) encompasses a constellation of findings that result in poor early graft function after transplant. This phenomenon is often the consequence of ischemia-reperfusion injury in the allograft and is not related to infection or rejection. It is characterized by a diffuse pattern of infiltrates on the chest x-ray and poor pulmonary gas exchange with $\text{PaO}_2:\text{FiO}_2$ ratios <300, with severe PGD characterized by diffuse severe infiltrates and a P:F ratio of <100 at 72 h posttransplant. Most cases of PGD are mild and self-limiting, resolving with supportive care. However, if the PGD is severe and worsening despite maximal medical therapy, diuresis, inotropic therapy, maximal ventilation support, and paralysis of the patient, mechanical circulatory support with ECMO can become necessary. The incidence of severe PGD has been steady over the past two decades at approximately 10–15% in most programs.

Bacterial, viral, and fungal infections are leading causes of morbidity and mortality in lung transplantation. The lung is one of the few solid organs that is in continuous contact with the environment. Each breath has the potential to introduce new organisms, and the reduced lymphatic function and mucociliary clearance in the transplanted lung increase the risk of serious infection. The highest incidence of infection is early after lung transplant and coincides with the intensity of immune suppression. Early infections, occurring within the first month after transplantation, are commonly bacterial (especially gram-negative bacilli) and manifest as pneumonia, mediastinitis, urinary tract infections, catheter sepsis, and skin infections. Patients

can develop pathogenic infections with organisms associated with pretransplant colonization, and perioperative antibiotic regimens are often deployed to address this. Viral infections, and CMV infections, in particular, can lead to severe recipient disease and early loss of graft and life. The majority of transplant programs employ antiviral prophylaxis in the early transplant period to avoid such complications. Invasive fungal infections peak in frequency between 10 days and 2 months after transplantation. Fungal prophylaxis regimens in the early posttransplant period vary widely. Treatment consists of inhaled amphotericin B in the setting of airway infection and/or azole therapy with more advanced or invasive disease. The institution of prophylaxis with oral trimethoprim-sulfamethoxazole (or inhalational pentamidine for sulfa-allergic patients) has effectively prevented *Pneumocystis* pneumonia. The risk of *Pneumocystis* infection is highest during the first year after transplant. However, as infections can also occur late after transplant, most centers recommend prophylactic therapy be continued for life.

LONG-TERM MANAGEMENT OF LUNG TRANSPLANT RECIPIENTS

While survival after lung transplantation continues to improve by era, the survival rates in this group are lower than in other solid-organ cohorts. Approximately 50% of lung transplant recipients will experience at least one episode of acute rejection in the first posttransplant year, and by 5 years posttransplant, approximately half will have developed chronic rejection. As a result, posttransplant immune suppression regimens may be more aggressive than in other solid-organ recipients, as described above. The immunosuppressive regimen must be balanced against the potential toxicities that accrue with these medications over time.

Acute cellular rejection in lung transplant recipients is most common in the first posttransplant year, with a decreased but not absent frequency thereafter. Infections can stimulate cellular rejection, most clearly demonstrated in the setting of CMV infection, but also noted after other infections. Most programs incorporate a schedule of routine surveillance bronchoscopy to assess for acute cellular rejection post-transplant. Acute cellular rejection manifests as a lymphocytic infiltrate involving the distal small vessels and capillaries and/or a lymphocytic bronchiolitis involving the distal airways of the lung. Acute cellular rejection, a risk factor for the development of chronic lung allograft dysfunction (CLAD), is treated with augmented immune suppression. Antibody-mediated rejection in its classic form is a neutrophilic vasculitis associated with the small vessels and capillaries of the lung, with associated deposition of by-products of the complement cascade, in the setting of allograft dysfunction and circulating donor-specific HLA antibodies in the blood. The manifestations of antibody-mediated rejection in the lung allograft are less specific than in other organs. Further research is ongoing into the diagnostic and treatment considerations of this entity in lung transplantation.

CLAD is an overarching description of the syndrome of long-term allograft rejection. The classic manifestation of CLAD is obliterative bronchiolitis, the development of fibrinous material within the distal airways that leads to small-airways obstruction. As transbronchial biopsies are insensitive for diagnosing obliterative bronchiolitis, a clinical diagnostic designation of bronchiolitis obliterans syndrome can be made when specific PFT criteria are met and other causes of PFT decline are excluded. CLAD can also present as a restrictive phenotype, with imaging demonstrating upper lobe-predominant pleural thickening, small lung volumes, and interstitial changes on high-resolution CT. Numerous therapies for CLAD have been utilized, including azithromycin, montelukast, extracorporeal photopheresis, alemtuzumab, and others, with varying degrees of success.

Infection is a significant complication of lung transplantation, with persistent risk over the lifetime of the transplant recipient. As time progresses, the chance of opportunistic infection increases. The risk of bacterial infection and fungal infection remains, and can affect the lung parenchyma, airways and anastomotic sites, and other organs. Viral infections such as CMV reactivation and infection, EBV-associated

TABLE 298-3 Predictors of Survival After Lung Transplantation

	1 YEAR SURVIVAL	10 YEAR SURVIVAL
Donor Factors	HCV donor	
Recipient Factors	Age <70 years Diagnosis other than pulmonary fibrosis, pulmonary hypertension, sarcoidosis, A1AT O_2 requirement <5 L CI >2 Outpatient at time of transplant Preserved recipient eGFR Total bilirubin <2	Age 18–35 years
Donor/Recipient Factors	Non female to male transplant Donor/recipient weight ratio >0.7	Higher levels of HLA matching
Operative Factors	Avoidance of unplanned conversion to cardiopulmonary bypass Decreased ischemic time	Bilateral lung transplant
Posttransplant Factors	$PaO_2/FIO_2 > 260$ at 72 h Absent need for postoperative ECMO support	Fewer hospitalizations for rejection
Other Factors	Higher center volume	Higher center volume

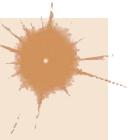
Abbreviations: A1AT, alpha-1 antitrypsin deficiency; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FIO₂, fraction of inspired oxygen; HCV, hepatitis C virus; PaO₂, partial pressure of oxygen.

posttransplant lymphoproliferative disease, and other rarer infections can also develop in the later posttransplant setting as well.

Numerous longer-term medical complications can be seen in lung transplant recipients. Essential hypertension, diabetes mellitus, chronic renal insufficiency, and bone loss are some examples of chronic medical conditions observed following transplantation. A multidisciplinary approach to care that involves the patient's primary care physician, local pulmonologist, and appropriate subspecialists, along with transplant pharmacy, as well as social work and care coordination, is beneficial in addressing the complex needs of lung transplant recipients over time. Predictors of short- and long-term outcomes after lung transplantation are outlined in **Table 298-3**.

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Interventional pulmonary medicine is a subspecialty of pulmonary and critical care medicine focusing on the evaluation and management of patients with thoracic malignancy, central airway obstruction, pleural disease, and advanced obstructive lung disease such as chronic obstructive pulmonary disease (COPD)/emphysema and asthma. Novel minimally invasive interventions have drastically changed the way we care for patients. In this chapter, we will summarize recent developments and evolving technologies in interventional pulmonology (IP).

DIAGNOSTIC BRONCHOSCOPY

With the introduction of the rigid bronchoscope by Gustav Killian in 1897, the mortality associated with foreign-body aspiration dropped from over 90% to less than 5%, as patients no longer had to suffer from airway obstruction and postobstructive pneumonia. Shigeto Ikeda developed the flexible bronchoscope in 1967, allowing access to the peripheral airways and lung parenchyma. Bronchoscopy has remained an important diagnostic and therapeutic procedure, and recent technology has significantly increased its utility.

ENDOBRONCHIAL ULTRASOUND

The diagnosis and staging of lung cancer remains one of the most important roles of advanced diagnostic bronchoscopy and IP. Convex endobronchial ultrasound (cEBUS) is a flexible bronchoscope combined with ultrasound technology that allows for real-time visualization during transbronchial needle aspiration (TBNA) of mediastinal and hilar lymph nodes and masses adjacent to the airways (**Fig. 299-1**).

With a sensitivity of 90% and a specificity of 100%, cEBUS has become the gold standard for lung cancer staging and can provide sufficient tissue to perform molecular profiling to guide targeted therapies in lung cancer with adequacy rates for testing that exceed 95%. cEBUS is also extremely helpful in diagnosing mediastinal and hilar adenopathy due to sarcoidosis and lymphoma.



FIGURE 299-1 Endobronchial ultrasound transbronchial needle aspiration image of needle under ultrasound guidance sampling station 4L lymph node. AO, aorta; PA, pulmonary artery.

PERIPHERAL BRONCHOSCOPY

Evaluations of pulmonary nodules and lung masses are frequent indications for bronchoscopy as a way to achieve a minimally invasive diagnosis. Historically, the diagnostic yield of bronchoscopy to target peripheral pulmonary lesions was approximately <60%. To improve on targeting success, multiple guidance platforms allow for more distal improved access in the periphery of the lung.

Smaller bronchoscopes that are <4 mm in diameter can be combined with available imaging tools to improve target localization. Radial-probe endobronchial ultrasound utilizes a radial scanning ultrasound probe that is inserted through the bronchoscope and into the lung, producing a real-time image of the target lesion. Electromagnetic navigation bronchoscopy (ENB) involves image-guidance systems that manipulate thin-slice CT images to create virtual airway reconstructions used as guided maps during bronchoscopy. Robotic-assisted bronchoscopic platforms offer the enhanced articulation and stability of a robotic arm replacing the traditional flexible bronchoscope. Additional studies are currently underway to explore further the utility of these systems for peripheral lesion biopsy.

THERAPEUTIC BRONCHOSCOPY

Therapeutic bronchoscopy is indicated for the relief of malignant and nonmalignant central airway obstruction, asthma, and emphysema. Active research is also focusing on the utility of bronchoscopy for the ablation of early-stage lung cancer, as well as the treatment of chronic bronchitis.

CENTRAL AIRWAY OBSTRUCTION

Central airway obstruction (CAO) describes obstruction of the trachea, main stem bronchi, bronchus intermedius, and/or lobar bronchi, and can present as intrinsic (endoluminal), extrinsic (extraluminal), or mixed (extraluminal tumor resulting in mass effect and endoluminal involvement) (Fig. 299-2). The differential diagnosis of CAO is shown in Table 299-1.

Patients often initially present with cough and exertional dyspnea, but then progress with increasing severity of obstruction to dyspnea at rest, stridor, and respiratory failure. Patients may also have wheezing, hemoptysis, or symptoms of postobstructive infection. Rigid bronchoscopy is the preferred tool to manage CAO in conjunction with ablative therapies, balloon bronchoplasty, and airway stenting to offer rapid symptomatic relief with immediate reductions in the level of required care. Therapeutic bronchoscopy for CAO has been shown to improve significantly both quality of life and survival.

TABLE 299-1 Differential Diagnosis of Central Airway Obstruction

MALIGNANT	NONMALIGNANT
Primary airway carcinoma	Lymphadenopathy
Bronchogenic	Sarcoidosis
Carcinoid adenoid cystic	Infectious (i.e., tuberculosis, histoplasmosis)
Mucoepidermoid	Cartilage
Metastatic carcinoma to the airway	Relapsing polychondritis
Bronchogenic	Granulation tissue from endotracheal tubes
Renal cell	Tracheostomy tubes
Breast	Airway stents
Thyroid	Foreign bodies
Colon	Surgical anastomosis
Sarcoma	Wegener's granulomatosis
Melanoma	Pseudotumor
Laryngeal carcinoma	Hamartomas
Esophageal carcinoma	Amyloid
Mediastinal tumors	Papillomatosis
Thymus	Hyperdynamic
Thyroid	Tracheomalacia
Germ cell	Bronchomalacia
Lymphadenopathy	Idiopathic
Lymphoma	Tuberculosis
	Sarcoidosis
	Other
	Foreign-body goiter
	Mucus plug
	Blood clot

ABLATIVE THERAPIES FOR CAO

Ablative therapy in the airway consists of both heat (laser, electrocautery, and argon plasma coagulation) and cold (cryotherapy) modalities. These techniques are most commonly used to destroy tumor and provide hemostasis. The cryoprobe can also be used for foreign-body removal. Other modalities, such as brachytherapy (BRT) and photodynamic therapy (PDT), have a delayed therapeutic effect and are often not suitable for situations where immediate relief of airway obstruction is desired.

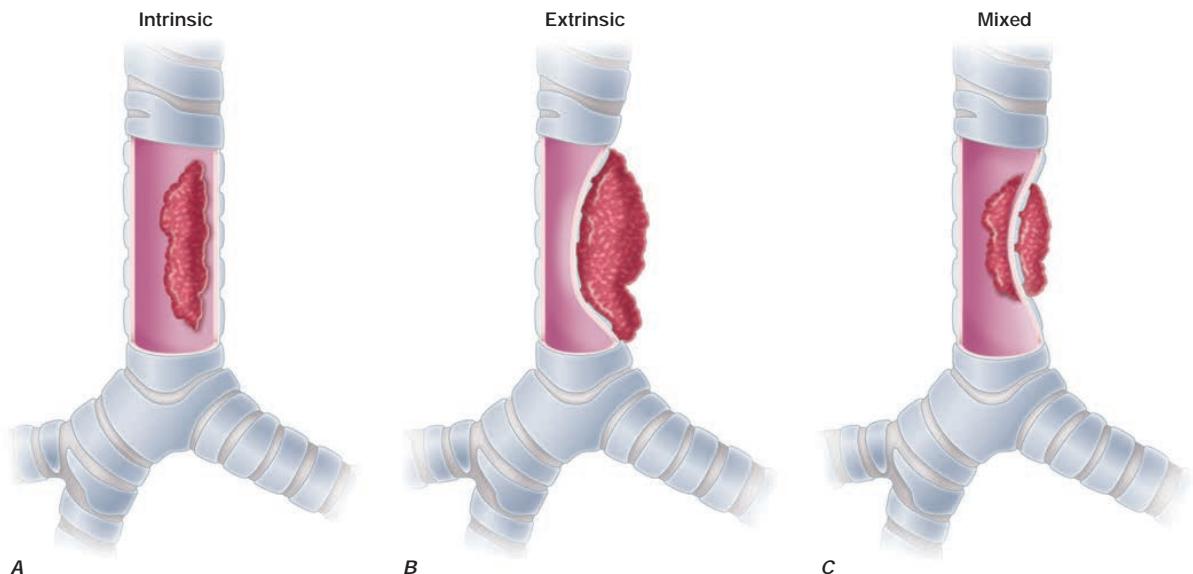


FIGURE 299-2 Types of central airway obstruction.

Bronchoplasty (or bronchial dilation) can be achieved with the barrel of the rigid bronchoscope or with balloons that can be passed via the rigid or flexible bronchoscope. Bronchoplasty is most commonly used for dilation of stenotic airways or disruption of webs related to nonmalignant causes of airway diseases. Although dilation generally leads to immediate relief of the stenosis, results can be short-lived and, hence, this technique is often combined with airway stenting. Complications are rare but can include airway tears if proper techniques are not followed.

AIRWAY STENTING

After airway patency is achieved, airway stents can be utilized to prevent recurrence of CAO. Reports of endoscopically implantable stents for the airways date back to 1914. Airway stents are commonly used to treat patients with CAO due to extrinsic compression from a variety of malignant and nonmalignant disorders. Stents are effective and lead to symptomatic relief in >90% of patients. A variety of airway stents are available, each with its own benefits and detriments; it is important to choose the right stent for the specific indication. Stent complications are not uncommon and include mucostasis, infection, and the development of granulation tissue. First-generation biodegradable stents, custom 3-dimensional-printed stents, and drug-coated stents are currently being evaluated, working toward a personalized medicine approach wherein stents are tailored to an individual's airway anatomy and underlying disease.

ENDOBRONCHIAL INTRATUMORAL CHEMOTHERAPY

Endobronchial intratumoral chemotherapy (EITC) is an intervention aimed at improving and/or maintaining airway patency in patients with malignant CAO, with the potential to eliminate the need for airway stenting and its associated complications. Under bronchoscopic guidance, high-dose therapeutics can be injected directly into tumor to enhance response and limit systemic side effects. Most recently, a novel microneedle injection catheter has been used to optimize drug delivery of paclitaxel, and was shown to be both feasible and safe with no restenosis. Additional studies are needed to assess the long-term effects of EITC.

ABLATIVE THERAPIES FOR EARLY-STAGE LUNG CANCER

Bronchoscopic ablation of early-stage lung cancer has long been described as the "holy grail" of bronchoscopy due to the appeal of staging, diagnosing, and treating biopsy-proven early-stage lung cancer in one procedural setting. There is limited experience with bronchoscopic radiofrequency ablation (B-RFA) and microwave ablation (MWA) as a potential means to treat early-stage lung cancer. Ultimately, the efficacy of bronchoscopic ablation of early-stage nonoperable lung cancer must be proven in longitudinal studies demonstrating noninferiority in survival as compared to the current gold standard of stereotactic body radiation (SBRT).

BRONCHOSCOPIC THERAPIES FOR ASTHMA

Bronchial thermoplasty (BT) is a treatment for patients with severe persistent asthma who remain symptomatic despite maximal medical treatment that delivers radiofrequency energy to the airways to reduce their smooth muscle mass. A pivotal randomized clinical trial did not show a change in FEV₁ or airway hyperresponsiveness, but was able to demonstrate an improvement in quality of life and reduction in exacerbation rates, visits to the emergency department, and days lost from school or work. At this time, the ideal asthma phenotypes and ideal candidates for this treatment modality remain to be determined.

BRONCHOSCOPIC THERAPIES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The National Emphysema Treatment Trial (NETT), published in 2003, demonstrated that lung volume reduction (LVR) surgery for severe emphysema confers improved survival and exercise capacity in patients with upper lobe-predominant disease and poor exercise capacity. At

the same time, it showed high perioperative morbidity and mortality. During the last decade, several bronchoscopic therapeutic modalities have been tested, including valves, coils, steam, stents, and foam, in patients with severe emphysema to mimic the physiologic effects of surgical lung volume reduction (SLVR) in a less invasive fashion.

BRONCHOSCOPIC LUNG VOLUME REDUCTION

Bronchoscopic lung volume reduction (BLVR) via valve placement involves placement of one-way valves in airways leading to areas of the lung with significant emphysema, allowing air and mucus to exit but blocking air entry to achieve lobar collapse. Several clinical trials on BLVR with valves have demonstrated improvements in lung function and overall improvement in quality of life and exercise tolerance. The overall safety profile of these valve systems compares favorably with surgical LVR with a much lower rate of perioperative morbidity and mortality.

TARGETED LUNG DENERVATION

Targeted lung denervation is a novel therapy that involves bronchoscopic ablation of peribronchial parasympathetic nerves in order to achieve permanent bronchodilation. Unlike bronchoscopic LVR, which focuses exclusively on patients with emphysema, targeted lung denervation is potentially applicable more broadly to all COPD patients, with studies showing a reduction in pulmonary exacerbations when compared with a sham denervated group.

PLEURAL INTERVENTIONS

Thoracic ultrasound has become invaluable in the evaluation of patients with pleural effusion and pneumothorax. Medical thoracoscopy (also called *pleuroscopy*) is a minimally invasive technique most commonly used to evaluate recurrent exudative pleural effusions, and is associated with a diagnostic yield of >95%.

Indwelling pleural catheters (IPCs) have gained tremendous popularity and have been declared by evidence-based guidelines to be as acceptable as chemical pleurodesis for the management of symptomatic malignant pleural effusions. When comparing IPC and pleurodesis via talc slurry, two multicentered, open-label, randomized controlled trials demonstrated IPC effectively relieved dyspnea, decreased the duration of hospital stay, and lessened the need for future procedures.

Pleural infection (empyema or complex parapneumonic effusion) is commonly encountered in clinical practice. The mainstay of therapy typically consisted of antibiotics, drainage of the infected pleural space with tube thoracostomy, and possible need for surgical decortication. The landmark Multicenter Intrapleural Sepsis Trial (MIST2) demonstrated that intrapleural sequential administration of rTPA and DNase resulted in significant radiographic and clinical improvements and allowed >90% of patients to avoid surgery.

PNEUMOTHORAX AND PERSISTENT AIR LEAK

Persistent air leak is defined as a nonresolving pneumothorax with an air leak lasting more than 5–7 days. For over a decade, the U.S. Food and Drug Administration has maintained a humanitarian device exemption for compassionate use of the Spiration Valve System for management of persistent air leak following lobectomy, segmentectomy, or LVR surgery, although the device has also been used "off label" for the treatment of persistent air leak due to primary and secondary spontaneous pneumothoraces.

SUMMARY

IP provides diagnostic and therapeutic options that span the spectrum of benign and malignant airway and pleural disorders. The constant innovations in diagnostic and treatment modalities have continued to help push the boundaries of pulmonary medicine.

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