14 - Pulmonary Disorders

Chapter 188. Approach to the Patient With Pulmonary Symptoms

Introduction

Key components in the evaluation of patients with pulmonary symptoms are the history, physical examination, and, in most cases, a chest x-ray. These components establish the need for subsequent testing, which may include pulmonary function testing and ABG analysis (see p. 1851), CT or other imaging test (see p. 1860), and bronchoscopy (see p. 1862).

History

The history can often establish whether symptoms of dyspnea, chest pain, wheezing, stridor, hemoptysis, and cough are likely to be pulmonary in origin. When more than one symptom occurs concurrently, the history should focus on which symptom is primary and whether constitutional symptoms, such as fever, weight loss, and night sweats, are also present. Other important information includes occupational and environmental exposures; family history, travel history, and contact history; previous illnesses and use of prescription, OTC, or illicit drugs; and previous test results (eg, tuberculin skin test, chest x-rays).

Physical Examination

Physical examination starts with assessment of general appearance. Discomfort and anxiety, body habitus, and the effect of talking or movement on symptoms (eg, inability to speak full sentences without pausing to breathe) all can be assessed while greeting the patient and taking a history and may provide useful information relevant to pulmonary status. Next, inspection, auscultation, and chest percussion and palpation are done.

Inspection: Inspection should focus on

- Signs of respiratory difficulty and hypoxemia (eg, restlessness, tachypnea, cyanosis, accessory muscle use)
- Signs of possible chronic pulmonary disease (eg, clubbing, pedal edema)
- Chest wall deformities
- Abnormal breathing patterns (eg, Cheyne-Stokes respiration, Kussmal's respirations)
- Jugular venous distention

Signs of hypoxemia include cyanosis (bluish discoloration of the lips, face, or nail beds), which signifies low arterial O_2 saturation (< 85%); the absence of cyanosis does not exclude the presence of hypoxemia.

Signs of respiratory difficulty include tachypnea and use of accessory respiratory muscles (sternocleidomastoids, intercostals, scalene) to breathe. Patients with COPD sometimes brace their arms against their legs or the examination table while seated (ie, tripod position) in a subconscious effort to provide more leverage to accessory muscles and thereby enhance respiration. Intercostal retractions (inward movement of the rib inter-spaces) are common among infants and older patients with severe airflow limitation; paradoxical breathing (inward motion of the abdomen during inspiration) signifies respiratory muscle fatigue or weakness.

Signs of possible chronic pulmonary disease include clubbing, barrel chest (the increased anterior-posterior diameter of the chest present in some patients with emphysema), and pursed lip breathing. Clubbing is enlargement of the fingertips (or toes) due to proliferation of connective tissue between the fingernail and the bone. Diagnosis is based on an increase in the profile angle of the nail as it exits the finger (to > 176°) or on an increase in the phalangeal depth ratio (to > 1—see

Fig. 188-1). "Sponginess" of the nail bed beneath the cuticle also suggests clubbing. Clubbing is most commonly observed in patients with lung cancer but is an important sign of chronic pulmonary disease, such as cystic fibrosis and idiopathic pulmonary fibrosis; it also occurs (but less commonly) in cyanotic heart disease, chronic infection (eg, infective endocarditis), stroke, inflammatory bowel disease, and cirrhosis. Clubbing occasionally occurs with osteoarthropathy and periostitis (primary or hereditary hypertrophic osteoarthropathy); in this instance, clubbing may be accompanied by skin changes, such as hypertrophied skin on the dorsa of the hands (pachydermoperiostosis), seborrhea, and coarse facial features. Digital clubbing can also occur as a benign hereditary abnormality that can be distinguished from pathologic clubbing by the absence of pulmonary symptoms or disease and by the presence of clubbing from an early age (by patient report).

Chest wall deformities, such as pectus excavatum and kyphoscoliosis, may restrict respirations and exacerbate symptoms of preexisting pulmonary disease.

[**Fig. 188-1.** Measuring finger clubbing.]

Abnormal breathing patterns cause fluctuations in respiratory rate so respiratory rate should be assessed and counted for 1 min.

- **Cheyne-Stokes respiration** (periodic breathing) is a cyclic fluctuation of respiratory rate and depth. From periods of brief apnea, patients breathe progressively faster and deeper (hyperpnea), then slower and shallower until they become apneic and repeat the cycle. Cheyne-Stokes respiration is most often caused by heart failure, a neurologic disorder (eg, stroke, advanced dementia), or drugs. The pattern in heart failure has been attributed to delays in cerebral circulation; respiratory centers lag in recognition of systemic acidosis/hypoxia (causing hyperpnea) or alkalosis/hypocapnia (causing apnea).

- **Biot's respiration** is an uncommon variant of Cheyne-Stokes respiration in which irregular periods of apnea alternate with periods in which 4 or 5 deep, equal breaths are taken. It differs from Cheyne-Stokes respiration in that it is characterized by abrupt starts and stops and lacks periodicity. It results from injury to the CNS and occurs in such disorders as meningitis.

- **Kussmaul's respirations** are deep, regular respirations caused by metabolic acidosis.

Jugular venous distention, sometimes observed during inspection, indicates an increase in right atrial and right ventricular pressure. The elevated pressure is usually caused by left ventricular dysfunction, but it may also be due to a pulmonary disorder causing pulmonary hypertension (see p. 1984). The presence of jugular venous distension should prompt a search for other signs of cardiac disorder (eg, 3rd heart sound [S_3 gallop], dependent edema).

Auscultation: Auscultation is arguably the most important component of the physical examination. All fields of the chest should be listened to, including the flanks, to detect abnormalities associated with each lobe of the lung. Features to listen for include

- Character and volume of breath sounds

- Presence or absence of vocal sounds

- Pleural friction rubs

- Ratio of inspiration to expiration (I:E ratio)

Cardiac auscultation (see p. 2020), conducted simultaneously with pulmonary auscultation, may reveal signs of pulmonary hypertension, such as a loud pulmonic 2nd heart sound (P_2), and of right heart failure, such as a right ventricular 4th heart sound (S_4) and tricuspid regurgitation.

The character and volume of breath sounds are useful in identifying pulmonary disorders. Vesicular

breath sounds are the normal sounds heard over most lung fields. Bronchial breath sounds are slightly louder, harsher, and higher pitched; they normally can be heard over the trachea and over areas of lung consolidation, such as occur with pneumonia.

Adventitious sounds are abnormal sounds, such as crackles, rhonchi, wheezes, and stridor.

- **Crackles** (previously called rales) are discontinuous adventitious breath sounds. Fine crackles are short high-pitched sounds; coarse crackles are longer-lasting low-pitched sounds. Crackles have been compared to the sound of crinkling plastic wrap and can be simulated by rubbing strands of hair together between 2 fingers near one's ear. They occur most commonly with atelectasis, alveolar filling processes (eg, pulmonary edema), and interstitial lung disease (eg, pulmonary fibrosis); they signify opening of collapsed alveoli.

- **Rhonchi** are low-pitched respiratory sounds that can be heard during inspiration or expiration. They occur in various conditions, including chronic bronchitis. The mechanism may relate to variations in obstruction as airways distend with inhalation and narrow with exhalation.

- **Wheezes** are whistling, musical breath sounds that are worse during expiration than inspiration. Wheezing can be a physical finding or a symptom and is usually associated with dyspnea.

- **Stridor** is a high-pitched, predominantly inspiratory sound formed by extrathoracic upper airway obstruction. It usually can be heard without a stethoscope. Stridor is usually louder than wheezing, is predominantly inspiratory, and is heard loudly over the larynx. It should trigger a concern for life-threatening upper airway obstruction.

- **Decreased breath sounds** signify poor air movement in airways, as occurs with asthma and COPD where bronchospasm or other mechanisms limit airflow. Breath sounds may also be decreased in the presence of a pleural effusion, pneumothorax, or obstructing endobronchial lesion.

Vocal sounds involve auscultation while patients vocalize.

- **Bronchophony** and **whispered pectoriloquy** occur when the patient's spoken or whispered voice is clearly transmitted through the chest wall. Voice transmission results from alveolar consolidation, as occurs with pneumonia.

- **Egophony** is said to occur when a patient says the letter "E" and the examiner hears the letter "A" on auscultation, again as occurs with pneumonia.

Friction rubs are grating or creaking sounds that fluctuate with the respiratory cycle and sound like skin rubbing against wet leather. They are a sign of pleural inflammation and are heard in patients with pleurisy or empyema and after thoracotomy.

I:E ratio is normally 1:2 but is prolonged to ≥ 1:3 when airflow is limited, such as in asthma and COPD, even in the absence of wheezing.

Percussion and palpation: Percussion is the primary physical maneuver used to detect the presence and level of pleural effusion. Finding areas of dullness during percussion signifies underlying fluid or, less commonly, consolidation.

Palpation includes tactile fremitus (vibration of the chest wall felt when a patient is asked to speak); it is decreased in pleural effusion and pneumothorax and increased in pulmonary consolidation (eg, lobar pneumonias). Point tenderness on palpation may signal underlying rib fracture or pleural inflammation.

In cor pulmonale (see p. 2132), a right ventricular impulse at the left lower sternal border may become evident and may be increased in amplitude and duration (right ventricular heave).

Chest Pain

Pulmonary, pleural, and chest wall disorders cause chest pain; examples are

- Pneumonia
- Pulmonary embolism
- Pleuritis
- Lung cancer
- Rib fractures

Cardiac, GI, and musculoskeletal disorders also cause chest pain. The evaluation of patients with chest pain is discussed on p. 2025.

Cough

Cough is an explosive expiratory maneuver that is reflexively or deliberately intended to clear the airways. It is the 5th most common symptom prompting physician visits.

Likely causes of cough (see Table 188-1) differ depending on whether the symptom is acute (< 3 wk) or chronic.

In acute cough, the most common causes are

- URI (including acute bronchitis)
- Postnasal drip
- COPD exacerbation
- Pneumonia

In chronic cough, the most common causes are

- Chronic bronchitis
- Postnasal drip
- Airway hyperresponsiveness after resolution of a viral or bacterial respiratory infection (ie, postinfection cough)
- Gastroesophageal reflux

The causes in children (see p. 2731) are similar to those in adults, but asthma and foreign body aspiration may be more common.

Very rarely, impacted cerumen or a foreign body in the external auditory canal triggers reflex cough through stimulation of the auricular branch of the vagus nerve. Psychogenic cough is even rarer and is a diagnosis of exclusion.

Evaluation

History: History of present illness should cover the duration and characteristics of the

[**Table 188-1.** Some Causes of Cough]

cough (eg, whether dry or productive of sputum or blood) and whether it is accompanied by dyspnea,

chest pain, or both.

Review of systems should seek symptoms of possible cause, including runny nose and sore throat (URI, postnasal drip); fever, chills, and pleuritic chest pain (pneumonia); night sweats and weight loss (tumor, TB); heartburn (gastroesophageal reflux); and difficulty swallowing or choking episodes while eating or drinking (aspiration).

Past medical history should note recent respiratory infections (ie, within previous 1 to 2 mo); history of allergies, asthma, COPD, and gastroesophageal reflux disease; risk factors for (or known) TB or HIV infection; and smoking history. Drug history should specifically include use of ACE inhibitors. Patients with chronic cough should be asked about exposure to potential respiratory irritants or allergens and travel to or residence in regions with endemic fungal illness.

Physical examination: Vital signs should be reviewed for the presence of tachypnea and fever.

General examination should look for signs of respiratory distress and chronic illness (eg, wasting, lethargy).

Examination of the nose and throat should focus on appearance of the nasal mucosa (eg, color, congestion) and presence of discharge (external or in posterior pharynx). Ears should be examined for triggers of reflex cough.

The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy.

A full lung examination is done, particularly including adequacy of air entry and exit; symmetry of breath sounds; and presence of crackles, wheezes, or both. Signs of consolidation (eg, egophony, dullness to percussion) should be sought.

Red flags: The following findings are of particular concern:

• Dyspnea

• Hemoptysis

• Weight loss

• Risk factors for TB or HIV infection

Interpretation of findings: Some findings point to particular diagnoses (see Table 188-1).

Other important findings are less specific. For example, the color (eg, yellow, green) and thickness of sputum do not help differentiate bacterial from other causes. Wheezing may occur with several causes. Hemoptysis in small amounts may occur with severe cough of many etiologies, although larger amounts of hemoptysis suggest bronchitis, bronchiectasis, TB, or primary lung cancer. Fever, night sweats, and weight loss may occur with many chronic infections as well as with cancer.

Testing: Patients with red flag findings of dyspnea or hemoptysis and patients in whom suspicion of pneumonia is high should have pulse oximetry and chest x-ray. Those with weight loss or risk factors should have chest x-ray and testing for TB and HIV infection.

For many patients without red flag findings, clinicians can base the diagnosis on history and physical examination findings and begin treatment without testing. For patients without a clear cause but no red flag findings, many clinicians empirically begin treatment for postnasal drip (eg, antihistamine and decongestant combinations, nasal corticosteroid sprays) or gastroesophageal reflux disease (eg, proton pump inhibitors, H_2 blockers). An adequate response to these interventions usually precludes the need for further evaluation.

Patients with chronic cough in whom presumptive treatment is ineffective should have a chest x-ray. If the

x-ray findings are unremarkable, many clinicians sequentially test for asthma (pulmonary function tests with methacholine challenge), sinus disease (sinus CT), and gastroesophageal reflux disease (esophageal pH monitoring). Sputum culture is helpful for patients with a possible indolent infection, such as pertussis, TB, or nontuberculous mycobacterial infection. Sputum cytology is noninvasive and should be done if cancer is suspected and the patient is producing sputum or having hemoptysis. Chest CT and possibly bronchoscopy should be done in patients in whom lung cancer or another bronchial tumor is suspected (eg, patients with a long smoking history, nonspecific constitutional signs) and in patients in whom empiric therapy has failed and who have inconclusive findings on preliminary testing.

Treatment

Treatment is management of the cause.

There is little evidence to support the use of cough suppressants or mucolytic agents. Coughing is an important mechanism for clearing secretions from the airways and can assist in recovery from respiratory infections. Therefore, although patients often expect or request cough suppressants, such treatment should be given with caution and reserved for patients with a URI and for patients receiving therapy for the underlying disorder for whom cough is still troubling.

Antitussives depress the medullary cough center (dextromethorphan and codeine) or anesthetize stretch receptors of vagal afferent fibers in bronchi and alveoli (benzonatate). Dextromethorphan, a congener of the opioid levorphanol, is effective as a tablet or syrup at a dose of 15 to 30 mg po 1 to 4 times/day for adults or 0.25 mg/kg po qid for children. Codeine has antitussive, analgesic, and sedative effects, but dependence is a potential problem, and nausea, vomiting, constipation, and tolerance are common adverse effects. Usual doses are 10 to 20 mg po q 4 to 6 h as needed for adults and 0.25 to 0.5 mg/kg po qid for children. Other opioids (hydrocodone, hydromorphone, methadone, morphine) have antitussive properties but are avoided because of high potential for dependence and abuse. Benzonatate, a congener of tetracaine that is available in liquid-filled capsules, is effective at a dose of 100 to 200 mg po tid.

Expectorants are thought to decrease viscosity and facilitate expectoration (coughing up) of secretions but are of limited benefit. Guaifenesin (200 to 400 mg po q 4 h in syrup or tablet form) is most commonly used because it has no serious adverse effects, but multiple expectorants exist, including bromhexine, ipecac, and saturated solution of K iodide (SSKI). Aerosolized expectorants such as N-acetylcysteine and DNAse are generally reserved for hospital-based treatment of cough in patients with bronchiectasis or cystic fibrosis. Ensuring adequate hydration may facilitate expectoration, as may inhalation of steam, although neither technique has been rigorously tested.

Topical treatments, such as acacia, licorice, glycerin, honey, and wild cherry cough drops or syrups (demulcents), are locally and perhaps emotionally soothing, but their use is not supported by scientific evidence.

Protussives, which stimulate cough, are indicated for such disorders as cystic fibrosis and bronchiectasis, in which a productive cough is thought to be important for airway clearance and preservation of pulmonary function. DNAse or hypertonic saline is given in conjunction with chest physical therapy and postural drainage to promote cough and expectoration. This approach is beneficial in cystic fibrosis but not in most other causes of chronic cough.

Bronchodilators, such as albuterol and ipratropium or inhaled corticosteroids, can be effective for cough after URI and in cough-variant asthma.

Key Points

• Danger signs include respiratory distress, chronic fever, weight loss, and hemoptysis.

• Clinical diagnosis is usually adequate.

• Occult gastroesophageal reflux disease should be remembered as a possible cause.

• Antitussives and expectorants should be used selectively.

Dyspnea

Dyspnea is unpleasant or uncomfortable breathing. It is experienced and described differently by patients depending on the cause.

Pathophysiology

Although dyspnea is a relatively common problem, the pathophysiology of the uncomfortable sensation of breathing is poorly understood. Unlike those for other types of noxious stimuli, there are no specialized dyspnea receptors, although recent MRI studies have identified a few specific areas in the midbrain that may mediate perception of dyspnea.

The experience of dyspnea likely results from a complex interaction between chemoreceptor stimulation, mechanical abnormalities in breathing, and the perception of those abnormalities by the CNS. Some authors have described the imbalance between neurologic stimulation and mechanical changes in the lungs and chest wall as neuromechanical uncoupling.

Etiology

Dyspnea has many pulmonary, cardiac, and other causes, which vary by acuity of onset (see Table 188-2).

The most common causes include

• Asthma

• Pneumonia

• COPD

• Myocardial ischemia

• Deconditioning

The most common cause of dyspnea in patients with chronic pulmonary or cardiac disorders is

• Exacerbation of their disease

However, such patients may also acutely develop another condition (eg, a patient with long-standing asthma may have an MI, a patient with chronic heart failure may develop pneumonia).

[**Table 188-2.** Some Causes of Dyspnea]

Evaluation

History: History of present illness should cover the duration, temporal onset (eg, abrupt, insidious), and provoking or exacerbating factors (eg, allergen exposure, cold, exertion, supine position). Severity can be determined by assessing the activity level required to cause dyspnea (ie, dyspnea at rest is more severe than dyspnea only with climbing stairs). For patients with baseline dyspnea, the physician should note how much dyspnea has changed from the patient's usual state.

Review of systems should seek symptoms of possible causes, including chest pain or pressure (pulmonary embolism [PE], myocardial ischemia, pneumonia); dependent edema, orthopnea, and paroxysmal nocturnal dyspnea (heart failure); fever, chills, cough, and sputum production (pneumonia); black, tarry stools or heavy menses (occult bleeding possibly causing anemia); and weight loss or night

sweats (cancer or chronic lung infection).

Past medical history should cover disorders known to cause dyspnea, including asthma, COPD, and heart disease, as well as risk factors for the different etiologies:

- Smoking history—for cancer, COPD, and heart disease
- Family history, hypertension, and high cholesterol levels—for coronary artery disease
- Recent immobilization or surgery, recent long-distance travel, cancer or risk factors for or signs of occult cancer, prior or family history of clotting, pregnancy, oral contraceptive use, calf pain, leg swelling, and known deep venous thrombosis—for PE

Occupational exposures (eg, gases, smoke, asbestos) should be investigated.

Physical examination: Vital signs are reviewed for fever, tachycardia, and tachypnea.

Examination focuses on the cardiovascular and pulmonary systems.

A full lung examination is done, particularly including adequacy of air entry and exit, symmetry of breath sounds, and presence of crackles, rhonchi, stridor, and wheezes. Signs of consolidation (eg, egophony, dullness to percussion) should be sought. The cervical, supraclavicular, and inguinal areas should be inspected and palpated for lymphadenopathy.

Neck veins should be inspected for distention, and the legs and presacral area should be palpated for pitting edema (both suggesting heart failure).

Heart sounds should be auscultated with notation of any extra heart sounds, muffled heart sounds, or murmur. Testing for pulsus paradoxus (a > 12-mm Hg drop of systolic BP during inspiration) can be done by inflating a BP cuff to 20 mm Hg above the systolic pressure and then slowly deflating until the first Korotkoff sound is heard only during expiration. As the cuff is further deflated, the point at which the first Korotkoff sound is audible during both inspiration and expiration is recorded. If the difference between the first and second measurement is > 12 mm Hg, then pulsus paradoxus is present.

Conjunctiva should be examined for pallor. Rectal examination and stool guaiac testing should be done.

Red flags: The following findings are of particular concern:

- Dyspnea at rest during examination
- Decreased level of consciousness or agitation or confusion
- Accessory muscle use and poor air excursion
- Chest pain
- Crackles
- Weight loss
- Night sweats

Interpretation of findings: The history and physical examination often suggest a cause and guide further testing (see Table 188-2). Several findings are of note. Wheezing (see p. 1847) suggests asthma or COPD. Stridor (see p. 1844) suggests extrathoracic airway obstruction (eg, foreign body, epiglottitis, vocal cord dysfunction). Crackles suggest left heart failure, interstitial lung disease, or, if accompanied by signs of consolidation, pneumonia.

However, the symptoms and signs of life-threatening conditions such as myocardial ischemia and PE can be nonspecific. Furthermore, the severity of symptoms is not always proportional to the severity of the cause (eg, PE in a fit, healthy person may cause only mild dyspnea). Thus, a high degree of suspicion for these common conditions is prudent. It is often appropriate to rule out these conditions before attributing dyspnea to a less serious etiology.

A clinical prediction rule (see Table 194-2 on p. 1912) can help estimate the risk of PE. Note that a normal O_2 saturation does not exclude PE.

Hyperventilation syndrome is a diagnosis of exclusion. Because hypoxia may cause tachypnea and agitation, it is unwise to assume every rapidly breathing, anxious young person merely has hyperventilation syndrome.

Testing: Pulse oximetry should be done in all patients, and a chest x-ray should be done as well unless symptoms are clearly caused by a mild or moderate exacerbation of a known condition. For example, patients with asthma or heart failure do not require an x-ray for each flare-up, unless clinical findings suggest another cause or an unusually severe attack. Most adults should have an ECG to detect myocardial ischemia (and serum cardiac marker testing if suspicion is high) unless myocardial ischemia can be excluded clinically.

In patients with severe or deteriorating respiratory status, ABGs should be measured to more precisely quantify hypoxemia, measure $PaCO_2$, diagnose any acid-base disorders stimulating hyperventilation, and calculate the alveolar-arterial gradient.

Patients who have no clear diagnosis after chest x-ray and ECG and are at moderate or high risk of having PE (from the clinical prediction rule—see Table 194-2 on p. 1912) should undergo ventilation/perfusion scanning or CT angiography. Patients who are at low risk may have D-dimer testing (to detect the presence of clot); a normal D-dimer level effectively rules out PE in a low-risk patient.

Chronic dyspnea may warrant additional tests, such as CT, pulmonary function tests, echocardiography, and bronchoscopy.

Treatment

Treatment is correction of the underlying disorder.

Hypoxemia is treated with supplemental O_2 as needed to maintain SaO_2 > 88% or PaO_2 > 55 mm Hg, because levels above these thresholds provide adequate O_2 delivery to tissues. Levels below these thresholds are on the steep portion of the O_2-Hb dissociation curve, in which small declines in arterial O_2 tension result in large declines in Hb saturation. O_2 saturation should be maintained at > 93% if myocardial or cerebral ischemia is a concern.

Morphine 0.5 to 5 mg IV helps reduce anxiety and the discomfort of dyspnea in various conditions, including MI, PE, and the dyspnea that commonly accompanies terminal illness. However, opioids can be deleterious in patients with acute airflow limitation (eg, asthma, COPD) because they suppress the ventilatory drive and worsen respiratory acidemia.

Key Points

- Pulse oximetry is a key component of the examination.
- Low O_2 saturation (< 90%) indicates a significant problem, but normal saturation does not rule one out.
- Accessory muscle use, low O_2 saturation, or decreased level of consciousness requires emergency evaluation and hospitalization.

• Myocardial ischemia and PE are relatively common, but symptoms and signs can be nonspecific.

• Exacerbation of known conditions (eg, asthma, COPD, heart failure) is common, but patients may also develop new problems.

Hyperventilation Syndrome

Hyperventilation syndrome is anxiety-related dyspnea and tachypnea often accompanied by systemic symptoms.

Hyperventilation syndrome most commonly occurs among young women but can affect either sex at any age. It is sometimes precipitated by emotionally stressful events. Hyperventilation syndrome is separate from panic disorder (see p. 1496), although the 2 conditions overlap; about half of patients with panic disorder have hyperventilation syndrome and one quarter of patients with hyperventilation syndrome have panic disorder. It occurs in both acute and chronic forms. Chronic hyperventilation is more common; however, the acute form is easier to recognize.

Symptoms and Signs

Patients with acute hyperventilation syndrome present with dyspnea sometimes so severe that they liken it to suffocation. It is accompanied by agitation and a sense of terror or by symptoms of chest pain, paresthesias (peripheral and perioral), peripheral tetany (eg, stiffness of fingers or arms), and presyncope or syncope or sometimes by a combination of all of these findings. Tetany occurs because respiratory alkalosis causes both hypophosphatemia and hypocalcemia. On examination, patients may appear anxious, tachypneic, or both; lung examination is unremarkable.

Patients with chronic hyperventilation syndrome present far less dramatically and often escape detection; they sigh deeply and frequently and often have nonspecific somatic symptoms in the context of mood and anxiety disorders and emotional stress.

Diagnosis

• Testing to exclude other diagnoses (chest x-ray, ECG, pulse oximetry)

Hyperventilation syndrome is a diagnosis of exclusion; the challenge is to use tests and resources judiciously to distinguish this syndrome from more serious diagnoses. Basic testing includes pulse oximetry, chest x-ray, and ECG. Pulse oximetry in hyperventilation syndrome shows O_2 saturation at or close to 100%. Chest x-ray is normal. ECG is done to detect cardiac ischemia, although hyperventilation syndrome itself can cause ST-segment depressions, T-wave inversions, and prolonged QT intervals. ABGs are needed when other causes of hyperventilation are suspected, such as metabolic acidosis. Occasionally, acute hyperventilation syndrome is indistinguishable from acute pulmonary embolism, and tests for pulmonary embolism (eg, D-dimer, ventilation/perfusion scanning, CT angiography) may be necessary.

Treatment

• Supportive counseling

• Sometimes psychiatric or psychologic treatment

Treatment is reassurance. Some physicians advocate teaching the patient maximal exhalation and diaphragmatic breathing. Most patients require treatment for underlying mood or anxiety disorders; such treatment includes cognitive therapy, stress reduction techniques, drugs (eg, anxiolytics, antidepressants, lithium), or a combination of these techniques.

Hemoptysis

Hemoptysis is coughing up of blood from the respiratory tract. Massive hemoptysis is production of ≥ 600 mL of blood (about a full kidney basin's worth) within 24 h.

Pathophysiology

Most of the lung's blood (95%) circulates through low-pressure pulmonary arteries and ends up in the pulmonary capillary bed, where gas is exchanged. About 5% of the blood supply circulates through high-pressure bronchial arteries, which originate at the aorta and supply major airways and supporting structures. In hemoptysis, the blood generally arises from this bronchial circulation, except when pulmonary arteries are damaged by trauma, by erosion of a granulomatous or calcified lymph node or tumor, or, rarely, by pulmonary arterial catheterization or when pulmonary capillaries are affected by inflammation.

Etiology

Blood-streaked sputum is common in many minor respiratory illnesses, such as URI and viral bronchitis.

The differential diagnosis is broad (see Table 188-3).

In adults, 70 to 90% of cases are caused by

• Bronchitis

• Bronchiectasis

• TB

• Necrotizing pneumonia

Primary lung cancer is an important cause in smokers ≥ 40 yr, but metastatic cancer rarely causes hemoptysis. Cavitary *Aspergillus* infection is increasingly recognized as a cause but is not as common as cancer.

In children, common causes are

• Lower respiratory tract infection

• Foreign body aspiration

Massive hemoptysis: The most common causes have changed over time and vary by geographic region but include the following:

• Bronchogenic carcinoma

• Bronchiectasis

• Tuberculous and other pneumonias

Evaluation

History: History of present illness should cover the duration and temporal patterns (eg, abrupt onset, cyclical recurrence), provoking factors (eg, allergen exposure, cold, exertion, supine position), and approximate volume of hemoptysis (eg, streaking, teaspoon, cup). Patients may need specific prompting to differentiate between true hemoptysis, pseudohemoptysis (ie, bleeding originating in the nasopharynx that is subsequently coughed up), and hematemesis. A sensation of postnasal drip or any bleeding from the nares without coughing is suggestive of pseudohemoptysis. Concomitant nausea and vomiting with

black, brown, or coffee-ground-colored blood is characteristic of hematemesis. Frothy sputum, bright red blood, and (if massive) a sensation of choking are characteristic of true hemoptysis.

Review of systems should seek symptoms suggesting possible causes, including fever and sputum production (pneumonia); night sweats, weight loss, and fatigue (cancer, TB); chest pain and dyspnea (pneumonia, pulmonary embolism); leg pain and leg swelling (pulmonary embolism); hematuria (Goodpasture's syndrome); and bloody nasal discharge (Wegener's granulomatosis).

Patients should be asked about risk factors for causes. These risk factors include HIV infection, use of immunosuppressants (TB, fungal infection); exposure to TB; long smoking history (cancer); and recent immobilization or surgery, known cancer, prior or family history of clotting, pregnancy, use of estrogen-containing drugs, and recent long-distance travel (pulmonary embolism).

Past medical history should cover known conditions that can cause hemoptysis, including chronic lung disease (eg, COPD, bronchiectasis, TB, cystic fibrosis), cancer, bleeding disorders, heart failure, thoracic aortic aneurysm, and pulmonary-renal syndromes (eg, Goodpasture's syndrome, Wegener's granulomatosis). Exposure to TB is important, particularly in patients with HIV infection or another immunocompromised state.

[**Table 188-3.** Some Causes of Hemoptysis]

A history of frequent nosebleeds, easy bruising, or liver disease suggests possible coagulopathy. The drug profile should be reviewed for use of anticoagulants and antiplatelet drugs.

Physical examination: Vital signs are reviewed for fever, tachycardia, tachypnea, and low O_2 saturation. Constitutional signs (eg, cachexia) and level of patient distress (eg, accessory muscle use, pursed lip breathing, agitation, decreased level of consciousness) should also be noted.

A full lung examination is done, particularly including adequacy of air entry and exit, symmetry of breath sounds, and presence of crackles, rhonchi, stridor, and wheezing. Signs of consolidation (eg, egophony, dullness to percussion) should be sought. The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy (suggesting cancer or TB).

Neck veins should be inspected for distention, and the legs and presacral area should be palpated for pitting edema (suggesting heart failure). Heart sounds should be auscultated with notation of any extra heart sounds or murmur that might support a diagnosis of heart failure and elevated pulmonary pressure.

The abdominal examination should focus on signs of hepatic congestion or masses, which could suggest either cancer or hematemesis from potential esophageal varices.

The skin and mucous membranes should be examined for ecchymoses, petechiae, telangiectasia, gingivitis, or evidence of bleeding from the oral or nasal mucosa.

If the patient can reproduce hemoptysis during examination, the color and amount of blood should be noted.

Red flags: The following findings are of particular concern:

• Massive hemoptysis

• Back pain

• Presence of a pulmonary artery catheter

• Malaise, weight loss, fatigue

• Extensive smoking history

• Dyspnea at rest during examination or absent or decreased breath sounds

Interpretation of findings: The history and physical examination often suggest a diagnosis and guide further testing (see Table 188-3).

Despite the many possibilities, some generalities can be made. A previously healthy person with a normal examination and no risk factors (eg, for TB, pulmonary embolism) who presents with acute-onset cough and fever most likely has hemoptysis due to an acute respiratory illness; chronic disorders are much lower on the list of possibilities. However, if risk factors are present, those specific disorders must be strongly suspected. A clinical prediction rule (see Table 194-2 on p. 1912) can help estimate the risk of pulmonary embolism. A normal O_2 saturation does not exclude pulmonary embolism.

Patients whose hemoptysis is due to a lung disorder (eg, COPD, cystic fibrosis, bronchiectasis) or heart disease (eg, heart failure) typically have a clear history of those disorders. Hemoptysis is not an initial manifestation.

Patients with known immunocompromise should be suspected of having TB or a fungal infection.

Patients with symptoms or signs of chronic illness but no known disorders should be suspected of having cancer or TB, although hemoptysis can be the initial manifestation of lung cancer in a patient who is otherwise asymptomatic.

Several specific findings are of note. Known renal failure or hematuria suggests a pulmonary-renal syndrome (eg, Goodpasture's syndrome, Wegener's granulomatosis). Patients with Wegener's granulomatosis may have nasal mucosal lesions. Visible telangiectasias suggest arteriovenous malformations. Patients with hemoptysis due to a bleeding disorder usually have cutaneous findings (petechiae, purpura, or both) or a history of anticoagulant or antiplatelet drug use. Recurrent hemoptysis coinciding with menses strongly suggests pulmonary endometriosis.

Testing: Patients with massive hemoptysis require treatment and stabilization, usually in an ICU, before testing. Patients with minor hemoptysis can undergo outpatient testing.

Imaging is always done. A chest x-ray is mandatory. Patients with normal results, a consistent history, and nonmassive hemoptysis can undergo empiric treatment for bronchitis. Patients with abnormal results and patients without a supporting history should undergo CT and bronchoscopy. CT may reveal pulmonary lesions that are not apparent on the chest x-ray and can help locate lesions in anticipation of bronchoscopy and biopsy. Ventilation/perfusion scanning or CT angiography can confirm the diagnosis of pulmonary embolism. CT and pulmonary angiography can also detect pulmonary arteriovenous fistulas.

Fiberoptic inspection of the pharynx, larynx, and airways may be indicated along with esophagogastric endoscopy when the etiology is obscure to distinguish hemoptysis from hematemesis and from nasopharyngeal or oropharyngeal bleeding.

Laboratory testing is also done. Patients usually should have a CBC, a platelet count, and measurement of PT and PTT. Anti-factor Xa testing can be used to detect supratherapeutic anticoagulation in patients receiving low mol wt heparin. Urinalysis should be done to look for signs of glomerulonephritis (hematuria, proteinuria, casts). TB skin testing and sputum culture should be done as the initial tests for active TB, but negative results do not preclude the need to induce sputum or do fiberoptic bronchoscopy to obtain samples for further acid-fast bacillus testing if an alternative diagnosis is not found.

Cryptogenic hemoptysis: The cause of hemoptysis remains unknown in 30 to 40% of patients, but the prognosis for patients with cryptogenic hemoptysis is generally favorable, usually with resolution of bleeding within 6 mo of evaluation.

Treatment

Massive hemoptysis: Initial treatment of massive hemoptysis has two objectives:

• Prevent aspiration of blood into the uninvolved lung (which can cause asphyxiation)

• Prevent exsanguination from ongoing bleeding

It can be difficult to protect the uninvolved lung because it is often initially unclear which side is bleeding. Once the bleeding side is identified, strategies include positioning the patient with the bleeding lung in a dependent position and selectively intubating and obstructing the bronchus going to the bleeding lung.

Prevention of exsanguination involves reversal of any bleeding diathesis and direct efforts to stop the bleeding. Clotting deficiencies can be reversed with fresh-frozen plasma and factor-specific or platelet transfusions. Laser therapy, cauterization, or direct injection with epinephrine or vasopressin can be done bronchoscopically.

Massive hemoptysis is one of the few indications for rigid (as opposed to flexible) bronchoscopy, which provides control of the airway, allows for a larger field of view than flexible bronchoscopy, allows better suctioning, and is more suited to therapeutic interventions, such as laser therapy.

Embolization of a pulmonary segment via bronchial artery catheterization is becoming the preferred method with which to stop massive hemoptysis, with reported success rates of up to 90%. Emergency surgery is indicated for massive hemoptysis not controlled by rigid bronchoscopy or embolization and is generally considered a last resort.

Once a diagnosis is made, further treatment is directed at the cause.

Minor hemoptysis: Treatment of minor hemoptysis is directed at the cause.

Early resection may be indicated for bronchial adenoma or carcinoma. Broncholithiasis (erosion of a calcified lymph node into an adjacent bronchus) may require pulmonary resection if the stone cannot be removed via rigid bronchoscopy. Bleeding secondary to heart failure or mitral stenosis usually responds to specific therapy for heart failure. In rare cases, emergency mitral valvulotomy is necessary for life-threatening hemoptysis due to mitral stenosis.

Bleeding from a pulmonary embolism is rarely massive and almost always stops spontaneously. If emboli recur and bleeding persists, anticoagulation may be contraindicated, and placement of an inferior vena cava filter is the treatment of choice.

Because bleeding from bronchiectatic areas usually results from infection, treatment of the infection with appropriate antibiotics and postural drainage is essential.

Key Points

• Hemoptysis needs to be distinguished from hematemesis and nasopharyngeal or oropharyngeal bleeding.

• Bronchitis, bronchiectasis, TB, and necrotizing pneumonia or lung abscess are the most common causes in adults.

• Lower respiratory tract infection and foreign body aspiration are the most common causes in children.

• Patients with massive hemoptysis require treatment and stabilization before testing.

• With massive hemoptysis, if the side of bleeding is known, patients should be positioned with the affected lung in the dependent position.

• Bronchial artery embolization is the preferred treatment for massive hemoptysis.

Solitary Pulmonary Nodule

A solitary pulmonary nodule is defined as a discrete lesion < 3 cm in diameter that is completely surrounded by lung parenchyma (ie, does not touch the hilum, mediastinum, or pleura and is without associated atelectasis or pleural effusion (for evaluation of a mediastinal mass, see p. 1993).

Solitary pulmonary nodules are most often detected incidentally when a chest x-ray is taken for other reasons. Nonpulmonary soft-tissue densities caused by nipple shadows, warts, cutaneous nodules, and bone abnormalities are often confused for a nodule on chest x-ray.

Etiology

Although cancer is usually the primary concern, solitary pulmonary nodules have many causes (see Table 188-4). Of these, the most common vary by age and risk factors, but typically include

• Granulomas

• Pneumonia

• Bronchogenic cysts

Evaluation

The primary goal of evaluation is to detect cancer and active infection.

[**Table 188-4.** Some Causes of a Solitary Pulmonary Nodule]

History: History may reveal information that suggests malignant and nonmalignant causes of a solitary pulmonary nodule and includes

• Current or past cigarette smoking

• History of cancer or an autoimmune disorder

• Occupational risk factors for cancer (eg, exposure to asbestos, vinyl chloride, radon)

• Travel to areas with endemic mycosis or high prevalence of TB

• Risk factors for opportunistic infections (eg, HIV, immune deficiency)

Older age, cigarette smoking, and history of cancer all increase the probability of cancer and are used along with the nodule diameter to estimate likelihood ratios for cancer (see Table 188-5).

Physical examination: A thorough physical examination may uncover findings that suggest an etiology (eg, a breast lump or skin lesion suggestive of cancer) for a pulmonary nodule but cannot definitely establish the cause.

Testing: The goal of initial testing is to estimate the malignant potential of the solitary pulmonary nodule. The first step is a review of plain x-rays and then usually CT.

Radiographic characteristics help define the malignant potential of a solitary pulmonary nodule:

• **Growth rate** is determined by comparison with previous chest x-ray or CT, if available. A lesion that has not enlarged in ≥ 2 yr suggests a benign etiology. Tumors that have volume doubling times from 21 to 400 days are likely to be malignant. Small nodules (< 1 cm) should be monitored at 3 mo, 6 mo, and then yearly for 2 yr.

• **Calcification** suggests benign disease, particularly if it is central (tuberculoma, histoplasmoma),

concentric (healed histoplasmosis), or in a popcorn configuration (hamartoma).

- **Margins** that are spiculated or irregular (scalloped) are more indicative of cancer.

- **Diameter** < 1.5 cm strongly suggests a benign etiology; diameter > 5.3 cm strongly suggests cancer. However, nonmalignant exceptions include lung abscess, Wegener's granulomatosis, and hydatid cyst.

These characteristics are sometimes evident on the original plain film but usually require CT. CT can also distinguish pulmonary from pleural radiopacities. CT has a sensitivity of 70% and a specificity of 60% for detecting cancer.

PET has an uncertain role in evaluation. It has a sensitivity > 90% and a specificity of about 78% for detecting cancer, but it is relatively new, and its role in evaluating pulmonary nodules is still being developed. False-negative PET scans can result from metabolically inactive tumors, and false-positive results can occur in various infectious and inflammatory conditions.

[Table 188-5. Estimating the Probability of Cancer in a Solitary Pulmonary Nodule]

Cultures may be useful when historical information suggests an infectious cause (eg, TB, coccidioidomycosis) as a possible diagnosis.

Invasive testing options include CT- or ultrasonography-guided transthoracic needle aspiration, fiberoptic bronchoscopy, and surgical biopsy. Although cancers can be diagnosed by biopsy, definitive treatment is resection, and so patients with a high likelihood of cancer with a resectable lesion should proceed to surgical resection. Transthoracic needle aspiration is best for peripheral lesions and is particularly useful if infectious etiologies are strongly considered because using the transthoracic approach, as opposed to bronchoscopy, avoids the possibility of contamination of the specimen with upper airway organisms. The main disadvantage of transthoracic needle aspiration is the risk of pneumothorax, which is about 10%. Fiberoptic bronchoscopy allows for endobronchial washing, brushing, needle aspiration, and transbronchial biopsy. Yield is higher for larger, more centrally located lesions, but very experienced operators using specially designed thin scopes can successfully biopsy peripheral lesions that are < 1 cm in diameter. In cases in which nodules are not accessible from these less invasive approaches, open surgical biopsy is necessary.

Treatment

- Sometimes surgery

- Sometimes observation

If the suspicion of cancer is very low, the lesions are very small (< 1 cm), or the patient refuses or is not a candidate for surgical intervention, observation is reasonable. Monitoring with follow-up at 3 mo, 6 mo, and then yearly for 2 yr is recommended. If the lesion has not grown for > 2 yr, it is likely benign.

When cancer is the most likely cause or when nonmalignant causes are unlikely, patients should undergo resection unless surgery is contraindicated due to poor pulmonary function, comorbidities, or withholding of consent.

Stridor

Stridor is a high-pitched, predominantly inspiratory sound. It is most commonly associated with acute disorders, such as foreign body aspiration but can be due to more chronic disorders, such as tracheomalacia.

Pathophysiology

Stridor is produced by the rapid, turbulent flow of air through a narrowed or partially obstructed segment of the extrathoracic upper airway. Involved areas include the pharynx, epiglottis, larynx, and the

extrathoracic trachea.

Etiology

Most causes manifest acutely, but some patients present with chronic or recurrent symptoms (see Table 188-6).

Acute causes are usually infectious except for foreign body and allergy. Chronic causes are usually a congenital or acquired structural abnormality of the upper airway.

Children: The most common causes of acute stridor in children include

• Croup

• Foreign body aspiration

Epiglottitis has historically been a common cause of stridor in children, but its incidence has decreased since the introduction of the *Haemophilus influenzae* type B (HiB) vaccine. Various congenital airway disorders can manifest as recurrent stridor in neonates and infants.

Adults: Common causes in adults include

• Vocal cord dysfunction

• Postextubation laryngeal edema

• Vocal cord edema or paralysis

• Laryngeal tumors

• Allergic reactions

Vocal cord dysfunction often mimics asthma, so many patients with vocal cord dysfunction are incorrectly given drugs for asthma but do not respond. Epiglottitis may be becoming more common among adults, but adults with epiglottitis are less likely than children to have stridor.

[**Table 188-6.** Some Causes of Stridor]

Evaluation

History: History of present illness should first identify whether symptoms are acute or chronic. If acute, any symptoms of URI (runny nose, fever, sore throat) or allergy (itching, sneezing, facial swelling, rash, potential allergen exposure) are noted. Recent intubation or neck surgery should be clinically obvious. If chronic, the age at onset (eg, since birth, since infancy, only in adulthood) and duration are determined, as well as whether symptoms are continuous or intermittent. For intermittent symptoms, provoking or exacerbating factors (eg, position, allergen exposure, cold, anxiety, feeding, crying) are sought. Important associated symptoms in all cases include cough, pain, drooling, respiratory distress, cyanosis, and difficulty feeding.

Review of systems should seek symptoms suggesting causative disorders, including heartburn or other reflux symptoms (laryngospasm); night sweats, weight loss, and fatigue (cancer); and voice change, trouble swallowing, and recurrent aspiration (neurologic disorders).

Past medical history in children should cover perinatal history, particularly regarding need for endotracheal intubation, presence of known congenital anomalies, and vaccination history (particularly HiB). In adults, history of prior endotracheal intubation, tracheotomy, recurrent respiratory infections, and tobacco and alcohol use should be elicited.

Physical examination: The first step is to determine the presence and degree of respiratory distress by evaluating vital signs (including pulse oximetry) and doing a quick examination. Signs of severe distress include cyanosis, decreased level of consciousness, low O_2 saturation (eg, < 90%), air hunger, use of accessory inspiratory muscles, and difficulty speaking. Children with epiglottitis may sit upright with arms braced on the legs or examination table, lean forward, and hyperextend the neck with the jaw thrust forward and mouth open in an effort to enhance air exchange (tripod position). Moderate distress is indicated by tachypnea, use of accessory muscles or respiration, and intercostal retractions. If distress is severe, further examination is deferred until equipment and personnel are arranged for emergency management of the airway.

Oropharyngeal examination of a patient (particularly a child) with epiglottitis may provoke anxiety, leading to functional obstruction and loss of the airway. Thus, if epiglottitis is suspected, a tongue depressor or other instrument should not be placed in the mouth. When suspicion is low and patients are in no distress, they may undergo imaging; others should be sent to the operating room for direct laryngoscopy, which should be done by an otolaryngologist with the patient under anesthesia.

If the patient's vital signs and airway are stable and acute epiglottitis is not suspected, the oral cavity should be thoroughly examined for pooled secretions, hypertrophic tonsils, in-duration, erythema, or foreign bodies. The neck is palpated for masses and tracheal deviation. Careful auscultation of the nose, oropharynx, neck, and chest may help discern the location of the stridor. Infants should be examined with special attention to craniofacial morphology (looking for signs of congenital malformations), patency of the nares, and cutaneous abnormalities.

Red flags: The following findings are of particular concern:

• Drooling and agitation

• Tripod position

• Cyanosis or hypoxemia on pulse oximetry

• Decreased level of consciousness

Interpretation of findings: The distinction between acute and chronic stridor is important. Other clinical findings are also often helpful (see Table 188-6).

Acute manifestations are more likely to reflect an immediately life-threatening disorder. With these disorders, fever indicates infection. Fever plus barking cough suggests croup or, very rarely, tracheitis. Patients with croup typically have more prominent URI symptoms and less of a toxic appearance. Fever without cough, particularly if accompanied by toxic appearance, sore throat, difficulty swallowing, or respiratory distress, suggests epiglottitis and, in young children, the less common retropharyngeal abscess. Drooling and the tripod position are suggestive of epiglottitis, whereas retropharyngeal abscess may manifest with neck stiffness and inability to extend the neck.

Patients without fever or URI symptoms may have an acute allergic reaction or aspirated foreign body. Acute allergic reaction severe enough to cause stridor usually has other manifestations of airway edema (eg, oral or facial edema, wheezing) or anaphylaxis (itching, urticaria). Foreign body obstruction of the upper airway that causes stridor is always acute but may be occult in toddlers (older children and adults can communicate the event unless there is near-complete airway obstruction, which will manifest as such, not as stridor). Cough is often present with foreign body but rare with allergic reaction.

Chronic stridor that begins early in childhood and without a clear inciting factor suggests a congenital anomaly or an upper airway tumor. In adults, heavy smoking and alcohol use should raise suspicion of laryngeal cancer. Vocal cord paralysis usually has a clear precipitant, such as surgery or intubation, or is associated with other neurologic findings, such as muscle weakness. Patients with tracheomalacia frequently have cough productive of sputum and have a history of recurrent respiratory infections.

Testing: Testing should include pulse oximetry. In patients with minimal respiratory distress, soft-tissue

neck x-rays may help. An enlarged epiglottis or retropharyngeal space can be seen on the lateral view, and the subepiglottic narrowing of croup (steeple sign) may be seen on the anteroposterior view. X-rays may also identify foreign objects in the neck or chest.

In other cases, direct laryngoscopy can detect vocal cord abnormalities, structural abnormalities, and tumors. CT of the neck and chest should be done if there is concern about a structural abnormality, such as an upper airway tumor or tracheomalacia. Flow-volume loops can be useful in chronic and intermittent stridor to show the presence of an upper airway obstruction. Abnormal flow-volume loop findings generally require follow up with CT or laryngoscopy.

Treatment

Definitive treatment of stridor involves treating the underlying disorder. As a temporizing measure in patients with severe distress, a mixture of helium and O_2 (heliox) improves airflow and reduces stridor in disorders of the large airways, such as postextubation laryngeal edema, croup, and laryngeal tumors. The mechanism of action is thought to be reduced flow turbulence as a result of lower density of helium compared with O_2 and nitrogen.

Nebulized racemic epinephrine (0.5 to 0.75 mL of 2.25% racemic epinephrine added to 2.5 to 3 mL of normal saline) and dexamethasone (10 mg IV, then 4 mg IV q 6 h) may be helpful in patients in whom airway edema is the cause.

Endotracheal intubation should be used to secure the airway in patients with advanced respiratory distress, impending loss of airway, or decreased level of consciousness. When significant edema is present, endotracheal intubation can be difficult, and emergency surgical airway measures (eg, cricothyrotomy, tracheostomy) may be required.

Key Points

- Inspiratory stridor is often a medical emergency.
- Assessment of vital signs and degree of respiratory distress is the first step.
- In some cases, securing the airway may be necessary before or in parallel with the physical examination.
- Acute epiglottitis is uncommon in children who have received HiB vaccine.

Vocal Cord Dysfunction

Paradoxical or dysfunctional movement of the vocal cords is defined as adduction of the true vocal cords on inspiration and abduction on expiration; it causes inspiratory airway obstruction and stridor that is often mistaken for asthma. Vocal cord paralysis (unilateral and bilateral) is discussed on p. 484. The general evaluation of patients with stridor is discussed on p. 1846.

Vocal cord dysfunction occurs more commonly among women aged 20 to 40. Etiology is unclear, but it appears to be associated with anxiety, depression, posttraumatic stress disorder, and personality disorders. It is not considered a factitious disorder (ie, patients are not doing it consciously).

Symptoms are usually inspiratory stridor and less often expiratory wheezing. Other manifestations can include hoarseness, throat tightness, a choking sensation, and cough.

Diagnosis is made by observing inspiratory closure of the vocal cords with direct laryngoscopy. Sometimes a diagnosis of vocal cord dysfunction is entertained only after patients have been misdiagnosed as having asthma and then not responded to bronchodilators or corticosteroids.

Treatment involves educating the patient about the nature of the problem; counseling from a speech therapist on special breathing techniques, such as panting, which can relieve episodes of stridor and

obstruction; and avoiding asthma misdiagnosis and treatment.

Vocal cord dysfunction associated with psychiatric diagnoses is often resistant to these measures. Referral for psychiatric counseling is indicated in these cases.

Wheezing

Wheezing is a relatively high-pitched whistling noise produced by movement of air through narrowed or compressed small airways. It is a symptom as well as a physical finding.

Pathophysiology

Airflow through a narrowed or compressed segment of a small airway becomes turbulent, causing vibration of airway walls; this vibration produces the sound of wheezing.

Wheezes are more common during expiration because increased intrathoracic pressure during this phase narrows the airways. Wheezing during expiration alone indicates milder obstruction than wheezing during both inspiration and expiration, which suggests more severe airway narrowing.

By contrast, turbulent flow of air through a narrowed segment of the large, extrathoracic airways produces a whistling inspiratory noise (stridor—see p. 1844).

Etiology

Small airway narrowing may be caused by bronchoconstriction, mucosal edema, or external compression, or partial obstruction by a tumor, foreign body, or thick secretions.

Overall, the most common causes are

• Asthma

• COPD

But wheezing may occur in other disorders affecting the small airways, including heart failure (cardiac asthma), anaphylaxis, and toxic inhalation. Sometimes, healthy patients manifest wheezing during a bout of acute bronchitis. In children, bronchiolitis and foreign body aspiration are also causes (see Table 188-7).

Evaluation

When patients are in significant respiratory distress, evaluation and treatment proceed at the same time.

History: History of present illness should determine whether the wheezing is new or recurrent. If recurrent, patients are asked the previous diagnosis and whether current symptoms are different in nature or severity. Particularly when the diagnosis is unclear, the acuity of onset (eg, abrupt or gradual), temporal patterns (eg, persistent vs intermittent, seasonal variations), and provoking or exacerbating factors (eg, current URI, allergen exposure, cold air, exercise, feeding in infants) are noted. Important associated symptoms include shortness of breath, fever, cough, and sputum production.

Review of systems should seek symptoms and signs of causative disorders, including fever, sore throat, and rhinorrhea (respiratory infection); orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema (heart failure); night sweats, weight loss, and fatigue (cancer); nasal congestion, itching eyes, sneezing, and rash (allergic reaction); and vomiting, heartburn, and swallowing difficulties (gastroesophageal reflux disease with aspiration).

Past medical history should ask about conditions known to cause wheezing, particularly asthma, COPD, and heart failure. Sometimes the patient's drug list may be the only indication of such diagnoses (eg, inhaled bronchodilators and corticosteroids in COPD; diuretics and ACE inhibitors in heart failure).

Patients with known disease should be asked about indicators of disease severity, such as previous hospitalization, intubation, or ICU admission. Also, conditions that predispose to heart failure are identified, including atherosclerotic or congenital heart disease and hypertension. Smoking history and exposure to secondhand smoke should be noted.

Physical examination: Vital signs are reviewed for presence of fever, tachycardia, tachypnea, and low O_2 saturation.

Any signs of respiratory distress (eg, accessory muscle use, intercostal retractions, pursed lip breathing, agitation, cyanosis, decreased level of consciousness) should be immediately noted.

Examination focuses on the lungs, particularly adequacy of air entry and exit, symmetry of breath sounds, and localization of wheezing (diffuse vs localized; inspiratory, expiratory, or both). Any signs of consolidation (eg, egophony, dullness to percussion) or crackles should be noted.

The cardiac examination should focus on findings that might indicate heart failure, such as murmurs, a 3rd heart sound (S_3 gallop), and jugular venous distention.

The nose and throat examination should note appearance of the nasal mucosa (eg, color, congestion), swelling of the face or tongue, and signs of rhinitis, sinusitis, or nasal polyps.

The extremities are examined for clubbing and edema, and the skin is examined for signs of allergic reactions (eg, urticaria, rash) or atopy (eg, eczema). The patient's general appearance is noted for constitutional signs, such as the cachexia and barrel chest of severe COPD.

Red flags: The following findings are of particular concern:

• Accessory muscle use, clinical signs of tiring, or decreased level of consciousness

• Fixed inspiratory and expiratory wheezing

• Swelling of the face and tongue (angioedema)

Interpretation of findings: Recurrent wheezing in a patient with a known history of

[**Table 188-7.** Some Causes of Wheezing]

disorders such as asthma, COPD, or heart failure is usually presumed to represent an exacerbation. In patients who have both lung and heart disease, manifestations may be similar (eg, neck vein distention and peripheral edema in cor pulmonale due to COPD and in heart failure), and testing is often required. When the cause is known asthma or COPD, a history of cough, postnasal drip, or exposure to allergens or to toxic or irritant gases (eg, cold air, dust, tobacco smoke, perfumes) may suggest a trigger.

Clinical findings help suggest a cause of wheezing in patients without a known history (see Table 188-7).

Acute (sudden-onset) wheezing in the absence of URI symptoms suggests an allergic reaction or impending anaphylaxis, especially if urticaria or angioedema is present. Fever and URI symptoms suggest infection: acute bronchitis in older children and adults and bronchiolitis in children < 2 yr. Crackles, distended neck veins, and peripheral edema suggest heart failure. Association of wheezing with feeding or vomiting in infants can be a result of gastroesophageal reflux.

Patients with asthma usually have paroxysmal or intermittent bouts of acute wheezing.

Persistent, localized wheezing suggests focal bronchial obstruction by a tumor or foreign body. Persistent wheezing manifesting very early in life suggests a congenital or structural abnormality. Persistent wheezing with sudden onset is consistent with foreign body aspiration, whereas the slowly progressive onset of wheezing may be a sign of extraluminal bronchial compression by a growing tumor or lymph node.

Testing: Testing seeks to assess severity, determine diagnosis, and identify complications.

- Pulse oximetry
- Chest x-ray (if diagnosis unclear)
- Sometimes ABG
- Sometimes pulmonary function testing

Severity is assessed by pulse oximetry and, in patients with respiratory distress or clinical signs of tiring, ABG testing. Patients known to have asthma usually have bedside peak flow measurements (or, when available, forced expiratory volume in 1 sec [FEV_1]).

Patients with new-onset or undiagnosed persistent wheezing should have a chest x-ray. X-ray can be deferred in patients with asthma who are having a typical exacerbation and in patients having an obvious allergic reaction. Cardiomegaly, pleural effusion, and fluid in the major fissure suggest heart failure. Hyperinflation and hyperlucency suggest COPD. Segmental or subsegmental atelectasis or infiltrate suggests an obstructing endobronchial lesion. Radiopacity in the airways or focal areas of hyperinflation suggest a foreign body.

If the diagnosis is unclear in patients with recurrent wheezing, pulmonary function testing can confirm airflow limitation and quantify its reversibility and severity. Methacholine challenge testing and exercise testing can confirm airway hyperreactivity in patients for whom the diagnosis of asthma is in question.

Treatment

Definitive treatment of wheezing is treatment of underlying disorders.

Wheezing itself can be relieved with inhaled bronchodilators (eg, albuterol 2.5 mg nebulized solution or 180 mg metered dose inhalation). Long-term control of persistent asthmatic wheezing may require inhaled corticosteroids and leukotriene inhibitors.

Intravenous H_2 blockers (diphenhydramine), corticosteroids (methylprednisolone), and subcutaneous and inhaled racemic epinephrine are indicated in cases of anaphylaxis.

Key Points

- Asthma is the most common cause, but not all wheezing is asthma.
- Acute onset of wheezing in a patient without a lung disorder may be due to aspiration, allergic reaction, or heart failure.
- Reactive airway disease can be confirmed via spirometry.
- Inhaled bronchodilators are the mainstay of acute treatment.

Chapter 189. Tests of Pulmonary Function

Introduction

Pulmonary function tests provide measures of airflow, lung volumes, gas exchange, response to bronchodilators, and respiratory muscle function. Basic pulmonary function tests available in the ambulatory setting include spirometry and pulse oximetry; these tests provide physiologic measures of pulmonary function and can be used to quickly narrow a differential diagnosis and suggest a subsequent strategy of additional testing or therapy. More complicated testing includes measurement of lung volumes; lung, chest wall, and respiratory system compliance (which requires measurement of esophageal pressure); and complete cardiopulmonary exercise testing. These tests provide a more detailed description of physiologic abnormalities and the likely underlying pathology. The choice and sequence of testing are guided by information taken from the history and physical examination.

Airflow, Lung Volumes, and Flow-Volume Loop

Airflow and lung volume measurements can be used to differentiate obstructive from restrictive pulmonary disorders, to characterize severity, and to measure responses to therapy. Measurements are typically reported as absolute flows and volumes and as percentages of predicted values using data derived from large populations of people presumed to have normal lung function. Variables used to predict normal values include age, sex, ethnicity, and height.

Airflow: Quantitative measures of inspiratory and expiratory flow are obtained by forced spirometry. Nose clips are used to occlude the nares.

In assessments of **expiratory flow**, patients inhale as deeply as possible, seal the lips around a mouthpiece, and exhale as forcefully and completely as possible into an apparatus that records the exhaled volume (forced vital capacity [FVC]) and the volume exhaled in the first second (the forced expiratory volume in 1 sec [FEV_1]—see Fig. 189-1). Most currently used devices measure only airflow and integrate time to estimate the expired volume.

In assessments of **inspiratory flow** and volume, patients exhale as completely as possible, then forcibly inhale. These maneuvers provide several measures. The FVC is the maximal amount of air that the patient can forcibly exhale after taking a maximal inhalation. The FEV_1 is the most reproducible flow parameter and is especially useful in diagnosing and monitoring patients with obstructive pulmonary disorders (eg, asthma, COPD).

The forced expiratory flow averaged over the time during which 25 to 75% of the FVC is exhaled may be a more sensitive marker of mild, small airway airflow limitation than the FEV_1, but the reproducibility of this variable is poor. The peak expiratory flow (PEF) is the peak flow occurring during exhalation. This variable is used primarily for home monitoring of patients with asthma and for determining diurnal variations in airflow.

Interpretation of these measures depends on good patient effort, which is often improved by coaching during the actual maneuver. Acceptable spiro-grams demonstrate good test initiation (eg, a quick and forceful onset of exhalation), no coughing, smooth curves, and absence of early termination of expiration (eg, minimum exhalation time of 6 sec with

[**Fig. 189-1.** Normal spirogram.]

no change in volume for the last 1 sec). Reproducible efforts agree within 5% or 100 mL with other efforts. Results not meeting these minimum acceptable criteria should be interpreted with caution.

Lung volume: Lung volumes (see Fig. 189-2) are measured by determining functional residual capacity (FRC) and with spirometry.

FRC is measured using gas dilution techniques or a plethysmograph (which is more accurate in patients who have airflow limitation and trapped gas).

Gas dilution techniques include

• Nitrogen washout

• Helium equilibration

With nitrogen washout, the patient exhales to FRC and then breathes from a spirometer containing 100% O_2. The test ends when the exhaled nitrogen concentration is zero. The collected volume of exhaled nitrogen is equal to 81% of the initial FRC.

With helium equilibration, the patient exhales to FRC and then is connected to a closed system containing known volumes of helium and O_2. Helium concentration is measured until it is the same on inhalation and exhalation, indicating it has equilibrated with the volume of gas in the lung, which can then be estimated from the change in helium concentration that has occurred.

Both of these techniques may underestimate FRC because they measure only the lung volume that communicates with the airways. In patients with severe airflow limitation, a considerable volume of trapped gas may communicate very poorly or not at all.

Body plethysmography uses Boyle's law to measure the compressible gas volume within the thorax and is more accurate than gas dilution techniques. While sitting in an airtight box, the patient tries to inhale against a closed mouthpiece from FRC. As the chest wall expands, the pressure in the closed box rises. Knowing the pre-inspiratory box volume and the pressure in the box before and after the inspiratory effort allows for calculation of the change in box volume, which must equal the change in lung volume.

Knowing FRC allows the lungs to be divided into subvolumes that are either measured with spirometry or calculated (see Fig. 189-2). Normally the FRC represents about 40% of total lung capacity (TLC).

Flow-volume loop: In contrast to the spiro-gram, which displays airflow (in L) over time (in sec), the flow-volume loop (see
Fig. 189-3) displays airflow (in L/sec) as it relates to lung volume (in L) during maximal inspiration from complete exhalation (residual volume [RV]) and during maximum expiration from complete inhalation (TLC). The principal advantage of the flow-volume loop is that it can show whether airflow is appropriate for a particular lung volume. For example, airflow is normally slower at low lung volumes. Because patients with pulmonary fibrosis have low lung volumes, airflow appears to be decreased if measured alone. However, when airflow is presented as a function of lung volume, it becomes apparent that airflow is actually higher than normal (as a result of the increased elastic recoil characteristic of fibrotic lungs).

[**Fig. 189-2.** Normal lung volumes.]

[
Table 189-1. Characteristic Physiologic Changes Associated with Pulmonary Disorders]

Flow-volume loops require that absolute lung volumes be measured. Unfortunately, many laboratories simply plot airflow against the FVC; the flow-FVC loop does not have an inspiratory limb and therefore does not provide as much information.

Patterns of Abnormalities

Most common respiratory disorders can be categorized as obstructive or restrictive on the basis of airflow and lung volumes (see Table 189-1).

Obstructive disorders: Obstructive disorders are characterized by a reduction in airflow, particularly the FEV_1 and the FEV_1 expressed as a percentage of the FVC (FEV_1/FVC). The degree of reduction in

FEV_1 compared with predicted values determines the degree of the obstructive defect (see Table 189-2). Obstructive defects are caused by

- Increased resistance to flow due to abnormalities within the airway lumen (eg, tumors, secretions, mucosal thickening)
- Changes in the wall of the airway (eg, contraction of smooth muscle, edema)
- Decreased elastic recoil (eg, the parenchymal destruction that occurs in emphysema)

With decreased airflow, expiratory times are longer than usual, and air may become trapped in the lungs due to incomplete emptying, thereby increasing lung volumes (eg, TLC, RV).

[**Table 189-2.** Severity of Obstructive and Restrictive Lung Disorders*]

[**Fig. 189-3.** Flow-volume loops.]

Improvement of FEV_1 and FEV_1/FVC by ≥ 12% or 200 mL with the administration of a bronchodilator confirms the diagnosis of asthma or airway hyperresponsiveness. However, some patients with asthma can have normal pulmonary function and normal spirometric parameters between exacerbations. When suspicion of asthma remains high despite normal spirometry results, provocative testing with methacholine, a synthetic analog of acetylcholine that is a nonspecific bronchial irritant, is indicated to detect or exclude bronchoconstriction. In a methacholine challenge test, spirometric parameters are measured at baseline and after inhalation of increasing concentrations of methacholine. Laboratories have different definitions of airway hyperreactivity, but in general patients showing at least a 20% drop in FEV_1 from baseline (PC_{20}) when the concentration of inhaled methacholine is < 1 mg/mL is considered diagnostic of increased bronchial reactivity, whereas a PC_{20} > 16 mg/mL excludes the diagnosis. PC_{20} values between 1 and 16 mg/mL are inconclusive.

Exercise testing may be used to detect exercise-induced bronchoconstriction but is less sensitive than methacholine challenge testing for detecting general airway hyperresponsiveness. The patient does a constant level of work on a treadmill or cycle ergometer for 6 to 8 min at an intensity selected to produce a heart rate of 80% of predicted maximum heart rate. The FEV_1 and FVC are measured before and 5, 15, and 30 min after exercise. Exercise-induced bronchospasm reduces FEV_1 or FVC ≥ 15% after exercise. Eucapnic voluntary hyperventilation (EVH) may also be used to diagnose exercise-induce bronchoconstriction and is the method accepted by the International Olympic Committee. EVH involves hyperventilation of a gas mixture of 5% CO_2 and 21% O_2 at 85% of maximum voluntary ventilation for 6 min. FEV_1 is then measured at specified intervals after the test. As with other bronchial provocation tests, the drop in FEV_1 that is diagnostic of exercise-induced bronchospasm varies by laboratory.

Restrictive disorders: Restrictive disorders are characterized by a reduction in lung volume, specifically a TLC < 80% of the predicted value. The decrease in TLC determines the severity of restriction (see Table 189-2). The decrease in lung volumes causes a decrease in airflow (reduced FEV_1—see Fig. 189-3B). However, airflow relative to lung volume is increased, so the FEV_1/FVC ratio is normal or increased.

Restrictive defects are caused by the following:

- Loss in lung volume (eg, lobectomy)
- Abnormalities of structures surrounding the lung (eg, pleural disorder, kyphosis, obesity)
- Weakness of the inspiratory muscles of respiration (eg, neuromuscular disorders)
- Abnormalities of the lung parenchyma (eg, pulmonary fibrosis)

The feature common to all is a decrease in the compliance of the lungs, the chest wall, or both.

Measurement of Gas Exchange

Gas exchange is measured through several means, including diffusing capacity for carbon monoxide, pulse oximetry, and arterial blood gas sampling.

Diffusing Capacity for Carbon Monoxide

The diffusing capacity for carbon monoxide (DLCO) is a measure of the ability of gas to transfer from the alveoli across the alveolar epithelium and the capillary endothelium to the RBCs. The DLCO depends not only on the area and thickness of the blood-gas barrier but also on the volume of blood in the pulmonary capillaries. The distribution of alveolar volume and ventilation also affects the measurement.

DLCO is measured by sampling end-expiratory gas for carbon monoxide (CO) after patients inspire a small amount of CO, hold their breath, and exhale. Measured DLCO should be adjusted for alveolar volume (which is estimated from dilution of helium) and the patient's Hct. DLCO is reported as mL/min/mm Hg and as a percentage of a predicted value.

Conditions that decrease DLCO: Conditions that primarily affect the pulmonary vasculature, such as primary pulmonary hypertension and pulmonary embolism, decrease DLCO. Conditions that affect the lung diffusely, such as emphysema and pulmonary fibrosis, decrease both DLCO and alveolar ventilation (V_A). Reduced DLCO also occurs in patients with previous lung resection because total lung volume is smaller, but DLCO corrects to or even exceeds normal when adjusted for V_A because increased additional vascular surface area is recruited in the remaining lung. Anemic patients have lower DLCO values that correct when adjusted for Hb.

Conditions that increase DLCO: DLCO may be higher than predicted in patients with heart failure, presumably because the increased pulmonary venous and arterial pressure recruits additional pulmonary microvessels. DLCO is also increased in patients with erythrocythemia, in part because of increased Hct and because of the vascular recruitment that occurs with increased pulmonary pressures due to increased viscosity. DLCO is increased in patients with alveolar hemorrhage because RBCs in the alveolar space can also bind CO. DLCO is also increased in patients with asthma. Although this increase is attributed to presumed vascular recruitment, recent data suggest it may also be due to growth factor-stimulated neovascularization.

Pulse Oximetry

Transcutaneous pulse oximetry estimates O_2 saturation (SpO_2) of capillary blood based on the absorption of light from light-emitting diodes positioned in a finger clip or adhesive strip probe. The estimates are generally very accurate and correlate to within 5% of measured arterial O_2 saturation (SaO_2). Results may be less accurate in patients with highly pigmented skin; patients wearing nail polish; and patients with arrhythmias, hypotension, or profound systemic vasoconstriction, in whom the amplitude of the signal may be dampened. Also, pulse oximetry is able to detect only oxyhemoglobin or reduced Hb but not other types of Hb (eg, carboxyhemoglobin, methemoglobin); those types are assumed to be oxyhemoglobin and falsely elevate the SpO_2 measurement.

Arterial Blood Gas Sampling

ABG sampling is done to obtain accurate measures of PaO_2, $PaCO_2$, and blood pH; these variables combined with the patient's temperature allow for calculation of HCO_3 level (which can also be measured directly from venous blood) and SaO_2. ABG sampling can also accurately measure carboxyhemoglobin and methemoglobin.

The radial artery is usually used. Because arterial puncture in rare cases leads to thrombosis and impaired perfusion of distal tissue, Allen's test is first done to ensure adequate collateral circulation. With this maneuver, the radial and ulnar pulses are simultaneously occluded until the hand becomes pale. The

ulnar pulse is then released while the pressure on the radial pulse is maintained. A blush across the entire hand within 7 sec of release of the ulnar pulse suggests adequate flow through the ulnar artery.

Under sterile conditions, a 22- to 25-gauge needle attached to a heparinized syringe is inserted just proximal to the maximal impulse of the radial arterial pulse and advanced slightly distally into the artery until pulsatile blood is returned. Systolic BP often pushes back the syringe plunger. After 3 to 5 mL of blood is collected, the needle is quickly withdrawn, and firm pressure is applied to the puncture site to facilitate hemostasis. Simultaneously, the ABG specimen is placed on ice to reduce O_2 consumption and CO_2 production by WBCs and is sent to the laboratory.

Oxygenation

Hypoxemia is a decrease in PO_2 in arterial blood; hypoxia is a decrease in the PO_2 in the tissue. ABGs accurately assess the presence of hypoxemia, which is generally defined as a PaO_2 low enough to reduce the SaO_2 below 90% (ie, PaO_2 < 60 mm Hg). Abnormalities in Hb (eg, methemoglobin), higher temperatures, lower pH, and higher levels of 2,3-diphosphoglycerate

[
Fig. 189-4. Oxyhemoglobin dissociation curve.]

reduce Hb O_2 saturation despite an adequate PaO_2, as indicated by the oxyhemoglobin dissociation curve (see Fig. 189-4).

Causes of hypoxemia can be classified based on whether the alveolar-arterial PO_2 gradient [(A-a)DO_2], defined as the difference between alveolar O_2 tension (PAO_2) and PaO_2, is elevated or normal. PAO_2 is calculated as follows:

$$P_{AO_2} = \left[F_{IO_2} \times \left(P_{atm} - P_{H_2O} \right) \right] - P_{aCO_2}/R$$

where FIO_2 is the fraction of inspired O_2 (eg, 0.21 at room air), P_{atm} is the ambient barometric pressure (eg, 760 mm Hg at sea level), PH_2O is the partial pressure of water vapor (eg, usually 47 mm Hg), $PaCO_2$ is the measured partial pressure of arterial CO_2, and R is the respiratory quotient, which is assumed to be 0.8 in a resting patient eating a normal diet.

For patients at sea level and breathing room air, FIO_2 = 0.21, and the (A-a)DO_2 can be simplified as follows:
(A - a)DO_2 = 150 - $PaCO_2$/0.8 - $PaCO_2$

where (A-a)DO_2 is typically < 20 but increases with age (because of age-related decline in pulmonary function) and with increasing FIO_2 (because, although Hb becomes 100% saturated at a PaO_2 of about 150 mm Hg, O_2 is soluble in blood, and the O_2 content of plasma continues to increase at increasing FIO_2). Estimations of normal (A-a)DO_2 values as < (2.5 + [FIO_2 × age in years]) or as less than the absolute value of the FIO_2 (eg, < 21 on room air; < 30 on 30% FIO_2) correct for these effects.

Hypoxemia with increased (A-a)DO_2: This situation is caused by

• Ventilation/perfusion (V/Q) mismatch

• Right-to-left shunting

• Severely impaired diffusing capacity

V/Q mismatch is one of the more common reasons for hypoxemia and contributes to the hypoxemia occurring with COPD and asthma. In normal lungs, regional perfusion closely matches regional ventilation

because of the arteriolar vasoconstriction that occurs in response to alveolar hypoxia. In disease states, dysregulation leads to perfusion of alveolar units that are receiving less than complete ventilation (V/Q mismatch). As a result, systemic venous blood passes through the pulmonary capillaries without achieving normal levels of PaO_2. Supplemental O_2 can correct hypoxemia due to V/Q mismatch by increasing the PaO_2, although the increased $(A\text{-}a)DO_2$ persists.

Right-to-left shunting is an extreme example of V/Q mismatch. With shunting, deoxygenated pulmonary arterial blood arrives at the left side of the heart without having passed through ventilated lung segments. Shunting may occur through lung parenchyma, through abnormal connections between the pulmonary arterial and venous circulations, or through intracardiac communications (eg, patent foramen ovale). Hypoxemia due to right-to-left shunting does not respond to supplemental O_2.

Impaired diffusing capacity only rarely occurs in isolation; usually it is accompanied by significant V/Q mismatch. Because O_2 completely saturates Hb after only a fraction of the time that blood is in contact with alveolar gas, hypoxemia due to impaired diffusing capacity occurs only when cardiac output is increased (eg, with exercise), when barometric pressure is low (eg, at high altitudes), or when > 50% of the pulmonary parenchyma is destroyed. As with V/Q mismatch, the $(A\text{-}a)DO_2$ is increased, but PaO_2 can be increased by increasing the FIO_2. Hypoxemia due to impaired diffusing capacity responds to supplemental O_2.

Hypoxemia with normal $(A\text{-}a)DO_2$: This situation is caused by

• Hypoventilation

• Low partial pressures of inspired O_2 (PIO_2)

Hypoventilation (reduced alveolar ventilation) decreases the PAO_2 and increases the $PaCO_2$, there by decreasing PaO_2. In cases of pure hypoventilation, the $(A\text{-}a)DO_2$ is normal. Causes of hypoventilation include decreased respiratory rate or depth (eg, due to neuromuscular disorders, severe obesity, or drug overdose) or an increase in the fraction of dead space ventilation in patients already at their maximal ventilatory limit (eg, an exacerbation of severe COPD). Hypoventilatory hypoxemia responds to supplemental O_2.

Decreased PIO_2 is a final uncommon cause of hypoxemia that in most cases occurs only at high altitude. Although FIO_2 does not change with altitude, ambient air pressure decreases exponentially; thus, PIO_2 decreases as well. For example, PIO_2 is only 43 mm Hg at the summit of Mt. Everest (altitude, 8848 m [29,028 ft]). The $(A\text{-}a)DO_2$ remains normal. Hypoxic stimulation of respiratory drive increases alveolar ventilation and decreases $PaCO_2$ level. This type of hypoxemia responds to supplemental O_2.

Carbon Dioxide

PCO_2 normally is maintained between 35 and 45 mm Hg. A dissociation curve similar to that for O_2 exists for CO_2 but is nearly linear over the physiologic range of $PaCO_2$. Abnormal PCO_2 is always linked to disorders of ventilation and is always associated with acid-base changes.

Hypercapnia: Hypercapnia is PCO_2 > 45 mm Hg. Causes of hypercapnia are the same as those of hypoventilation (see above). Disorders that increase CO_2 production (eg, hyperthyroidism, fever) when combined with an inability to increase ventilation also cause hypercapnia.

Hypocapnia: Hypocapnia is PCO_2 < 35 mm Hg. Hypocapnia is always caused by hyperventilation due to pulmonary (eg, pulmonary edema or embolism), cardiac (eg, heart failure), metabolic (eg, acidosis), drug-induced (eg, aspirin, progesterone), CNS (eg, infection, tumor, bleeding, increased intracranial pressure), or physiologic (eg, pain, pregnancy) disorders or conditions. Hypocapnia is thought to directly increase bronchoconstriction and lower the threshold for cerebral and myocardial ischemia, perhaps

through its effects on acid-base status.

Carboxyhemoglobinemia

CO binds to Hb with an affinity 210 times that of O_2 and prevents O_2 transport. Clinically toxic carboxyhemoglobin levels are most often the result of exposure to exhaust fumes or from smoke inhalation, although cigarette smokers have detectable levels. Patients with CO poisoning (see p. 3334) may present with nonspecific symptoms such as malaise, headache, and nausea. Because poisoning often occurs during colder months (because of indoor use of combustible fuel heaters), symptoms may be confused with a viral syndrome such as influenza. Clinicians must be alert to the possibility of CO poisoning and measure levels of carboxyhemoglobin when indicated; COHb can be directly measured from venous blood—an arterial sample is unnecessary.

Treatment is the administration of 100% O_2 (which shortens the half-life of carboxyhemoglobin) and sometimes the use of a hyperbaric chamber.

Methemoglobinemia

Methemoglobin is Hb in which the iron is oxidized from its ferrous (Fe^{2+}) to its ferric (Fe^{3+}) state. Methemoglobin does not carry O_2 and shifts the normal HbO_2 dissociation curve to the left, thereby limiting the release of O_2 to the tissues. Methemoglobinemia is caused by certain drugs (eg, dapsone, local anesthetics, nitrates, primaquine, sulfonamides) or, less commonly, by certain chemicals (eg, aniline dyes, benzene derivatives). Methemoglobin level can be directly measured by co-oximetry (which emits 4 wavelengths of light and is capable of detecting methemoglobin, COHb, Hb, and HbO_2) or may be estimated by the difference between the O_2 saturation calculated from the measured PaO_2 and the directly measured SaO_2. Patients with methemoglobinemia most often have asymptomatic cyanosis. In severe cases, O_2 delivery is reduced to such a degree that symptoms of tissue hypoxia result, such as confusion, angina, and myalgias. Stopping the causative drug or chemical exposure is often sufficient. Rarely, methylene blue (a reducing agent; a 1% solution is given 1 to 2 mg/kg slowly IV) or exchange transfusion is needed.

Tests of Respiratory Muscle Function

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) measurements may aid in evaluating respiratory muscle weakness.

MIP is the pressure generated during maximal inspiratory effort against a closed system. It is usually measured at residual volume (RV) because inspiratory muscle strength is inversely related to lung volume (in a curvilinear fashion).

MEP is measured during a similar maneuver at total lung capacity (TLC) because expiratory muscle strength is directly related to lung volume (again in a curvilinear fashion). The information available from these maneuvers is nonspecific, however, and cannot distinguish between insufficient effort, muscle weakness, and a neurologic disorder.

The **maximal voluntary ventilation** (MVV) is another measure of the neuromuscular and respiratory systems. The MVV is the total volume of air exhaled during 12 sec of rapid, deep breathing, which can be compared with a predicted MVV defined as the forced expiratory volume in 1 sec (FEV_1) × 35 or 40. A significant difference between the predicted and measured MVV may indicate insufficient neuromuscular reserve, abnormal respiratory mechanics, or an inadequate effort. Progressive reduction of tidal volumes during the test is consistent with neuromuscular abnormalities but also occurs with gas trapping as a result of disorders that cause airflow limitation.

The **sniff test** is sometimes used in suspected cases of diaphragmatic paralysis or paresis. During continuous fluoroscopic examination, the patient makes a quick, short, strong inspiratory effort ("sniff"). This maneuver minimizes the contribution of the other muscles of respiration (eg, intercostals). A

weakened hemidiaphragm may have decreased excursion compared with the contralateral diaphragm or may move upward paradoxically. Occasionally, electromyographic interrogation of the diaphragm and phrenic nerve is done but is of uncertain diagnostic accuracy. Muscle and nerve biopsies may be helpful in selected cases.

Exercise Testing

The two most common forms of exercise testing used to evaluate pulmonary disorders are the 6-min walk test and full cardiopulmonary exercise testing.

Six-minute walk test: This simple test measures the maximal distance that patients can walk at their own pace in 6 min. The test assesses global functional capacity but does not provide specific information on the individual systems involved in exercise capacity (ie, cardiac, pulmonary, hematologic, musculoskeletal). Neither does it assess patient effort. This test is used for preoperative and postoperative evaluation of patients undergoing lung transplantation and lung volume reduction surgery, to monitor response to therapeutic interventions and pulmonary rehabilitation, and to predict mortality and morbidity in patients with cardiac and pulmonary vascular disorders.

Cardiopulmonary exercise testing (CPET): This computerized test provides a breath-by-breath analysis of respiratory gas exchange and cardiac function at rest and during a period of exercise, the intensity of which is increased incrementally until symptoms limit testing. Information on airflow, O_2 consumption, CO_2 production, and heart rate are collected and used for computation of other variables; ABGs may also be sampled. Exercise is done on a treadmill or on a bicycle ergometer; the ergometer may be preferable because work rate can be directly measured.

CPET primarily determines whether patients have normal or reduced maximal exercise capacity (VO_2max) and, if so, suggests probable causes. CPET is used to define which organ systems contribute to a patient's symptoms of exertional dyspnea and exercise intolerance and to what extent. The test is also more sensitive for detecting early or subclinical disease than are less comprehensive tests that are done at rest. Examples of applications include

- Assessment of exercise capacity for disability evaluation
- Preoperative assessment
- Determination of whether dyspnea symptoms result from cardiac or pulmonary problems in patients who have disorders of both organ systems
- Selection of candidates for cardiac transplantation
- Assessment of prognosis in selected disorders (eg, heart disease, pulmonary vascular disorders, and cystic fibrosis)

CPET can also help gauge responses to therapeutic interventions and guide prescription of exercise in rehabilitation programs. In following the response to therapy or disease progression, a steady-state CPET involving at least 6 min of constant work at 50 to 70% of the maximal work rate achieved during a maximal CPET may be more useful than an incremental, maximal CPET. Repeated evaluation at this work rate over time provides comparable data and is sensitive to improvement or decline in cardiopulmonary function.

Several variables are assessed during CPET, and no single one is diagnostic of a cause for exercise limitation. Instead, an integrative approach using clinical data, trends during exercise, and recognition of underlying patterns of physiologic responses is used.

Chapter 190. Diagnostic and Therapeutic Pulmonary Procedures

Introduction

Diagnostic tests besides pulmonary function testing (see p. 1851) include various types of chest imaging, electrocardiography, and ventilation/perfusion scanning. Diagnostic procedures include bronchoscopy, mediastinoscopy and mediastinotomy, pleural biopsy, thoracentesis, thoracoscopy and video-assisted thoracoscopic surgery, thoracotomy, transthoracic needle biopsy, and tube thoracostomy. Pulmonary artery catheterization is discussed elsewhere (see p. 2248). Therapeutic procedures include chest physiotherapy and pulmonary rehabilitation.

Chest Imaging

Imaging includes use of x-rays, MRI, nuclear scanning, and ultrasonography. There are no absolute contraindications to undergoing noninvasive imaging procedures.

X-Ray Techniques

X-ray techniques that are used to image the chest include plain x-rays, fluoroscopy, high-resolution and helical (spiral) CT, and CT angiography.

Chest x-ray: Plain chest x-rays and fluoroscopy are used to provide images of the lungs and surrounding structures.

Plain chest x-rays provide images of structures in and around the thorax and are most useful for identifying abnormalities in the heart, lung parenchyma, pleura, chest wall, diaphragm, mediastinum, and hilum. They are usually the initial test done to evaluate the lungs. The standard chest x-ray is taken from back to front (posteroanterior view) to minimize x-ray scatter that could artifactually enlarge the cardiac silhouette and from the side of the thorax (lateral view). Lordotic or oblique views can be obtained to evaluate pulmonary nodules or to clarify abnormalities that may be due to superimposed structures, although chest CT provides more information and has largely superseded these views. Lateral decubitus views may be used to distinguish free-flowing from loculated pleural effusion, but again CT provides more information. End-expiratory views can be used to detect small pneumothoraces. Screening chest x-rays are often done but are almost never indicated; one exception is in asymptomatic patients with positive tuberculin skin test results, in whom a single posteroanterior chest x-ray without a lateral view is used to make decisions regarding treatment for pulmonary TB. Portable (usually anteroposterior) chest x-rays are almost always suboptimal and should be used only when patients are too ill to be transported to the radiology department.

Chest fluoroscopy is the use of a continuous x-ray beam to image movement. It is useful for detecting unilateral diaphragmatic paralysis. During a sniff test, in which the patient is instructed to forcibly inhale through the nose (or sniff), a paralyzed hemidiaphragm moves cranially (paradoxically) while the unaffected hemidiaphragm moves caudally.

Computed tomography: CT defines intrathoracic structures and abnormalities more clearly than does a chest x-ray. Conventional (planar) CT provides multiple 10-mm-thick cross-sectional images through the thorax. Its main advantage is wide availability. Disadvantages are motion artifact and limited detail from volume averaging of tissue within each 10-mm slice.

High-resolution CT (HRCT) provides 1-mm-thick cross-sectional images. HRCT is particularly helpful in evaluating interstitial lung diseases (eg, lymphangitic carcinomatosis, sarcoid, fibrosing alveolitis) and bronchiectasis.

Helical (spiral) CT provides multiplanar images of the entire chest as patients hold their breath for 8 to 10 sec while being moved continuously through the CT gantry. Helical CT is thought to be at least equivalent to conventional CT for most purposes. Its main advantages are speed, less radiation exposure, and an ability to construct 3-dimensional images. Software can also generate images of bronchial mucosa (virtual bronchoscopy). Its main disadvantages are less availability and the requirement for breath-

holding, which can be difficult for patients with symptomatic pulmonary disease.

CT angiography uses a bolus of IV contrast to highlight the pulmonary arteries, which is useful in diagnosis of pulmonary embolism. Dye load is comparable to conventional angiography, but the test is quicker and less invasive. Several studies have confirmed sufficient accuracy of CT angiography for the detection of pulmonary emboli, so it has largely replaced ventilation/perfusion (V/Q) scanning and conventional pulmonary angiography (except in patients unable to tolerate contrast).

Magnetic Resonance Imaging

MRI has a relatively limited role in pulmonary imaging but is preferred over CT in specific circumstances, such as assessment of superior sulcus tumors, possible cysts, and other lesions that abut the chest wall. In patients with suspected pulmonary embolism in whom IV contrast cannot be used, MRI can sometimes identify large proximal emboli but usually is limited in this disorder. The use of MRI to evaluate pulmonary hypertension is being studied, and this practice may become more common.

Advantages include absence of radiation exposure, excellent visualization of vascular structures, lack of artifact from bone, and excellent soft-tissue contrast. Disadvantages include respiratory and cardiac motion and the time it takes to do the procedure.

Ultrasonography

Ultrasonography is primarily used to facilitate procedures such as thoracentesis and central venous catheter insertion. Endobronchial ultrasonography is sometimes used in conjunction with fiberoptic bronchoscopy to help localize masses and enlarged lymph nodes. Ultrasonography is also useful for evaluating presence and size of pleural effusions.

Nuclear Scanning

Nuclear scanning techniques used to image the chest include ventilation/perfusion (V/Q) scanning and positron emission tomography (PET) scanning.

V/Q scanning: V/Q scanning uses inhaled radionuclides to detect ventilation and IV radionuclides to detect perfusion. Areas of ventilation without perfusion, perfusion without ventilation, or matched increases and decreases in both can be detected with 6 to 8 views of the lungs.

V/Q scanning is most commonly used for diagnosing pulmonary embolism but has largely been replaced by CT angiography. Split-function ventilation scanning, in which the degree of ventilation is quantified for each lobe, is used to predict the effect of lobar or lung resection on pulmonary function; post-surgical forced expiratory volume in 1 sec (FEV_1) is estimated as the percentage of uptake of ventilation tracer in the healthy fraction of the lungs multiplied by preoperative FEV_1 (in liters). A value of < 0.8 L (or < 40% of that predicted for the patient) indicates limited pulmonary reserve and a high likelihood of unacceptably high perioperative morbidity and mortality.

PET scanning: PET scanning uses radioactively labeled glucose (fluorodeoxyglucose) to measure metabolic activity in tissues. It is used in pulmonary disorders to determine whether lung nodules or mediastinal lymph nodes harbor tumor (metabolic staging) and whether cancer is recurrent in previously irradiated, scarred areas of the lung. PET is superior to CT for mediastinal staging because PET can identify tumor in normal-sized lymph nodes and at extrathoracic sites, thereby decreasing the need for invasive procedures such as mediastinoscopy and needle biopsy. Current spatial resolution of PET is 7 to 8 mm; thus, the test is not useful for lesions < 1 cm. PET reveals metastatic disease in up to 14% of patients in whom it would not otherwise be suspected. The sensitivity of PET (80 to 95%) is comparable to that of histologic tissue examination. False-positive results can occur with inflammatory lesions, such as granulomas; slowly growing tumors (eg, bronchoalveolar carcinoma, carcinoid tumor, some metastatic cancers) may cause false-negative results. Newer combined CT-PET scanners may become the most cost-effective technology for lung cancer diagnosis and staging.

Electrocardiography

Electrocardiography is a useful adjunct to other pulmonary tests because it provides information about the right side of the heart (see p. 2054) and therefore pulmonary disorders such as chronic pulmonary hypertension and pulmonary embolism.

Chronic pulmonary hypertension leading to chronic right atrial and ventricular hypertrophy and dilation may manifest as prominent P waves (P pulmonale) and ST-segment depression in leads II, III, and aVF; rightward shift in QRS axis; inferior shift of the P wave vector; and decreased progression of R waves in precordial leads.

COPD patients commonly have low voltage due to interposition of hyperexpanded lungs between the heart and ECG electrodes.

Pulmonary embolism (submassive or massive) may cause acute right ventricle overload or failure, which manifests as right axis deviation (R > S in V_1), with S-wave deepening in lead I, Q-wave deepening in lead III, and ST-segment elevation and T-wave inversion in lead III and the precordial leads ($S_1Q_3T_3$ pattern). Right bundle branch block also sometimes occurs.

Bronchoscopy

Bronchoscopy is introduction of an endoscope into the airways. Flexible fiberoptic bronchoscopy has replaced rigid bronchoscopy for virtually all diagnostic, and most therapeutic, indications.

Rigid bronchoscopy is now used only when a wider aperture and channels are required for better visualization and instrumentation such as when

- Investigating vigorous pulmonary hemorrhage (in which the rigid bronchoscope can better identify the bleeding source and, with its larger suction channel, can better suction the blood and prevent asphyxiation)
- Viewing and removing aspirated foreign bodies in young children
- Viewing obstructive endobronchial lesions (requiring laser debulking or stent placement)

Flexible bronchoscopes are nearly all color video-compatible, facilitating airway visualization and documentation of findings.

Diagnostically, flexible fiberoptic bronchoscopy allows for

- Direct airway visualization down to, and including, subsegmental bronchi
- Sampling of respiratory secretions and cells via bronchial washings, brushings, and lavage of peripheral airways and alveoli
- Biopsy of endobronchial, parenchymal, and mediastinal structures

Therapeutic uses include suctioning of retained secretions, endobronchial stent placement, and balloon dilation of airway stenoses.

Contraindications: Absolute contraindications include

- Untreatable life-threatening arrhythmias
- Inability to adequately oxygenate the patient during the procedure
- Acute respiratory failure with hypercapnia (unless the patient is intubated and ventilated)

Relative contraindications include

• Uncooperative patient

• Recent MI

• High-grade tracheal obstruction

• Uncorrectable coagulopathy

Transbronchial biopsy should be done with caution in patients with uremia, superior vena cava obstruction, or pulmonary hypertension because of increased risk of bleeding. Inspection of the airways is safe in these patients, however.

Procedure: Bronchoscopy should be done only by a pulmonologist or trained surgeon in a monitored setting, typically a bronchoscopy suite, operating room, or ICU (for ventilated patients).

Patients should receive nothing by mouth for at least 4 h before bronchoscopy and have IV access, intermittent BP monitoring, continuous pulse oximetry, and cardiac monitoring. Supplemental O_2 should be available. Premedication with atropine 0.01 mg/kg IM or IV to decrease secretions and vagal tone is common, although this practice has been called into question by recent studies. Shortacting benzodiazepines, opioids, or both are generally given to patients before the procedure to decrease anxiety, discomfort, and cough.

The pharynx and vocal cords are anesthetized with nebulized or aerosolized lidocaine (1 or 2%, to a maximum of 250 to 300 mg for a 70-kg patient). The bronchoscope is lubricated with lidocaine jelly and passed through the nostril or through the mouth with use of an oral airway or bite block. After inspecting the nasopharynx and larynx, the clinician passes the bronchoscope through the vocal cords during inspiration, into the trachea and then further distally into the bronchi.

Several ancillary procedures can be done as needed, with or without fluoroscopic guidance:

• **Bronchial washing:** Saline is injected through the bronchoscope and subsequently aspirated from the airways.

• **Bronchial brushing:** A brush is advanced through the bronchoscope and used to abrade suspicious lesions to obtain cells.

• **Bronchoalveolar lavage:** 50 to 200 mL of sterile saline is infused into the distal bronchoalveolar tree and subsequently suctioned out, retrieving cells, protein, and microorganisms located at the alveolar level. Local areas of pulmonary edema created by lavage may cause transient hypoxemia.

• **Transbronchial biopsy:** Forceps are advanced through the bronchoscope and airway to obtain samples from one or more sites in the lung parenchyma. Transbronchial biopsy can be done without x-ray guidance, but evidence supports increased diagnostic yields and lower incidence of pneumothorax when fluoroscopic guidance is used.

• **Transbronchial needle aspiration:** A retractable needle is inserted through the bronchoscope and can be used to sample enlarged mediastinal lymph nodes or masses.

Patients are typically given supplemental O_2 and observed for 2 to 4 h after the procedure. Return of a gag reflex and maintenance of O_2 saturation when not receiving O_2 are the two primary indices of recovery. Standard practice is to obtain a posteroanterior chest x-ray after transbronchial lung biopsy to exclude pneumothorax.

Complications: Serious complications are uncommon; minor bleeding from a biopsy site and fever occur in 10 to 15% of patients. Premedication can cause oversedation with respiratory depression, hypotension, and cardiac arrhythmias. Rarely, topical anesthesia causes laryngospasm, bronchospasm,

seizures, methemoglobinemia with refractory cyanosis, or cardiac arrhythmias or arrest.

Bronchoscopy itself may cause minor laryngeal edema or injury with hoarseness, hypoxemia in patients with compromised gas exchange, arrhythmias (most commonly premature atrial contractions, ventricular premature beats, or bradycardia), and, very rarely, transmission of infection from suboptimally sterilized equipment. Mortality is 1 to 4/10,000 patients. The elderly and patients with serious comorbidities (severe COPD, coronary artery disease, pneumonia with hypoxemia, advanced cancers, mental dysfunction) are at greatest risk.

Transbronchial biopsy can cause pneumothorax (2 to 5%) and significant hemorrhage (1 to 1.5%); mortality increases to 12/10,000 patients, but doing the procedure can avoid the need for thoracotomy.

Mediastinoscopy and Mediastinotomy

Mediastinoscopy is introduction of an endoscope into the mediastinum. Mediastinotomy is surgical opening of the mediastinum. The two are complementary. Mediastinotomy gives direct access to aortopulmonary window lymph nodes, which are inaccessible by mediastinoscopy. Both procedures are done to evaluate or excise mediastinal lymphadenopathy or masses and to stage cancers (eg, lung cancer, esophageal cancer), although PET scanning is decreasing the need for these procedures for cancer staging.

Contraindications: Contraindications include the following:

• Superior vena cava syndrome

• Previous mediastinal irradiation

• Mediastinoscopy

• Median sternotomy

• Tracheostomy

• Aneurysm of the aortic arch

Mediastinoscopy and mediastinotomy are done by surgeons in an operating room using general anesthesia. For mediastinoscopy, the soft tissue of the neck is bluntly dissected down to the trachea and distally to the carina through an incision in the suprasternal notch. A mediastinoscope is inserted into the space allowing access to the paratracheal, tracheobronchial, azygous, and subcarinal nodes and to the superior posterior mediastinum. Anterior mediastinotomy (the Chamberlain procedure) is surgical entry to the mediastinum through an incision in the parasternal 2nd left intercostal space, allowing access to anterior mediastinal and aortopulmonary window lymph nodes, common sites of metastases for left upper lobe lung cancers.

Complications: Complications occur in < 1% of patients and include bleeding, infection, vocal cord paralysis due to recurrent laryngeal nerve damage, chylothorax from duct injury, and pneumothorax.

Pleural Biopsy

Pleural biopsy is done to determine the cause of an exudative pleural effusion when thoracentesis is not diagnostic. The yield of closed pleural biopsy is about twice as high for TB than it is for pleural cancers. Improved laboratory techniques, newer diagnostic tests for pleural fluid (eg, adenosine deaminase levels, interferon-γ, PCR studies for suspected TB), and more widespread availability of thoracoscopy have made the procedure less necessary.

Percutaneous pleural biopsy should be done only by a pulmonologist or surgeon trained in the procedure and should be done only in patients who are cooperative and have no coagulation abnormalities. Technique is essentially the same as that for thoracentesis and can be done at the bedside; no specific

additional patient preparation is necessary. At least 3 specimens obtained from one skin location, with 3, 6, and 9 o'clock positioning of the needle-cutting chamber, are needed for histology and culture.

Chest x-ray should be done after biopsy because of increased risk of complications, which are the same as those for thoracentesis but with higher incidence of pneumothorax and hemorrhage.

Thoracentesis

Thoracentesis is puncture through the chest wall for the purpose of aspirating pleural fluid. It is used to determine the etiology of a pleural effusion (diagnostic thoracentesis), to relieve dyspnea caused by pleural fluid (therapeutic thoracentesis), and, occasionally, to carry out pleurodesis.

Contraindications: No **absolute contraindications** to thoracentesis exist except refusal of or inability to consent to the procedure.

Relative contraindications include

• Uncertain fluid location by examination

• Minimal fluid volume

• Altered chest wall anatomy

• Pulmonary disease severe enough to make complications life threatening

• Bleeding diatheses or coagulopathy

• Uncontrolled coughing

Procedure: Thoracentesis can be safely done at the patient's bedside or in an outpatient setting. Presence and location of pleural fluid is verified by physical examination (chest percussion) or by imaging techniques. Ultrasonography, CT, or both may be useful if chest x-rays are equivocal, if prior thoracentesis attempts were unsuccessful, or if the fluid is loculated.

Thoracentesis is best done with the patient sitting upright and leaning slightly forward with arms supported. Recumbent or supine thoracentesis (eg, in a ventilated patient) is possible but best done with ultrasound or CT guidance. Only unstable patients and patients at high risk of decompensation due to complications require monitoring (eg, pulse oximetry, ECG).

Under sterile conditions, 1 to 2% lidocaine is injected with a 25-gauge needle to anesthetize the skin. A larger (20- or 22-gauge) needle with anesthetic is then inserted at the upper border of the rib one intercostal space below the fluid level in the midscapular line. The needle is advanced with periodic aspiration (to avoid inadvertent insertion into a blood vessel and intravascular injection), and anesthetic is injected at progressively deeper levels. The most painful level after the skin is the parietal pleura, which should be infiltrated the most. The needle is then advanced beyond the parietal pleura until pleural fluid is aspirated, at which point the depth of the needle should be noted. A large-bore (16- to 19-gauge) thoracentesis needle-catheter device is then attached to a 3-way stopcock, which is connected to a 30- to 50-mL syringe and tubing that drains into a container. The thoracentesis needle is passed through the skin and subcutaneous tissue along the upper border of the rib into the effusion at about the same depth noted during anesthesia. The catheter is inserted through the needle, and the needle is withdrawn to decrease the risk of pneumothorax.

Pleural fluid can then be aspirated and, with a turn of the stopcock, collected in tubes or bags for further evaluation. Fluid should be removed in stages not to exceed 1.5 L/day because hypotension and pulmonary edema may occur with removal of > 1.5 L of fluid at one sitting or with rapid evacuation of the pleural space using a vacuum or suction bottle. When large volumes of fluid must be removed, blood pressure should be monitored continuously.

It has been standard practice to obtain a chest x-ray after thoracentesis to rule out pneumothorax, document the extent of fluid removal, and view lung fields previously obscured by fluid, but evidence suggests that routine chest x-ray is not necessary in asymptomatic patients.

Coughing is common as the lung re-expands; it does not signify pneumothorax. If the pleural process is inflammatory, pleuritic pain, an audible pleural rub, or both may develop as fluid is removed because of approximation of inflamed visceral and parietal pleura. When substantial volumes of fluid are removed from the pleural space, the plunger on the syringe should be released periodically during aspiration. If the fluid in the syringe is drawn back into the pleural space when negative pressure on the syringe is decreased, pleural pressure may be too negative, and the lung may be restricted from re-expanding because of enveloping adhesions or tumor.

Complications: Complications include

• Pneumothorax

• Hemoptysis due to lung puncture

• Re-expansion pulmonary edema or hypotension after rapid removal of large volumes of fluid

• Hemothorax due to damage to intercostal vessels

• Puncture of the spleen or liver

• Vasovagal syncope

Bloody fluid that does not clot in a collecting tube indicates that blood in the pleural space was not iatrogenic, because free blood in the pleural space rapidly defibrinates.

Thoracoscopy and Video-Assisted Thoracoscopic Surgery

Thoracoscopy is introduction of an endoscope into the pleural space. Thoracoscopy can be used for visualization (pleuroscopy) or for surgical procedures. Surgical thoracoscopy is more commonly referred to as video-assisted thoracoscopic surgery (VATS). Pleuroscopy can be done with the patient under conscious sedation in an endoscopy suite, whereas VATS requires general anesthesia and is done in the operating room. Both procedures induce a pneumothorax to create a clear view.

Thoracoscopy is used to evaluate exudative effusions and various pleural and lung lesions when noninvasive testing is inconclusive. The diagnostic accuracy for malignant and tuberculous disease of the pleura is 95%. The procedure is also used for pleurodesis in patients with recurrent malignant effusions and to break up loculations in patients with empyema.

Indications for VATS include correction of spontaneous primary pneumothorax, bullectomy and lung volume reduction surgery in emphysema, wedge resection, and, in some medical centers, lobectomy and even pneumonectomy. Less common indications are excision of benign mediastinal masses; biopsy and staging of esophageal cancer; sympathectomy for severe hyperhidrosis or causalgia; and repair of traumatic injuries to the lung, pleura, and diaphragm.

Contraindications: Contraindications are the same as those for thoracentesis; adhesive obliteration of the pleural space is an absolute contraindication. Biopsy is contraindicated in patients with highly vascular cancers, severe pulmonary hypertension, and severe bullous lung disease.

Procedure: Although some pulmonologists do pleuroscopy, VATS is done by thoracic surgeons. Both procedures are similar to chest tube insertion; a trocar is inserted into an intercostal space through a skin incision, through which a thoracoscope is inserted. Additional incisions permit the use of video cameras and accessory instruments.

After thoracoscopy, a chest tube is usually required for 1 to 2 days.

Complications: Complications are similar to those of thoracentesis. Postprocedural fever is common (16%); pleural tears causing air leak, subcutaneous emphysema, or both are less common (2% each). Hemorrhage, lung perforation, and gas embolism are serious but rare.

Thoracotomy

Thoracotomy is surgical opening of the chest. It is done to evaluate and treat pulmonary problems when noninvasive procedures are nondiagnostic or unlikely to be definitive.

Contraindications: Contraindications are those general to surgery and include coagulopathy that cannot be corrected, acute cardiac ischemia, and instability or insufficiency of major organ systems.

Procedure: Three basic approaches are used.

- Limited anterior or lateral thoracotomy: A 6- to 8-cm intercostal incision is made to approach the anterior structures.

- Posterolateral thoracotomy: The posterolateral approach gives access to pleurae, hilum, mediastinum, and the entire lung.

- Sternal splitting incision (median sternotomy): When access to both lungs is desired, as in lung volume reduction surgery, a sternal splitting incision is used.

Patients undergoing limited thoracotomy require a chest tube for 1 to 2 days and in many cases can leave the hospital in 3 to 4 days. The principal indications for thoracotomy are lobectomy and pneumonectomy (eg, lung cancer surgery). Video-assisted thoracoscopic surgery has replaced thoracotomy for open pleural and lung biopsies.

Complications: Complications are greater than those for any other pulmonary biopsy procedure because of the risks of general anesthesia, surgical trauma, and a longer hospital stay with more postoperative discomfort. Hemorrhage, infection, pneumothorax, bronchopleural fistula, and reactions to anesthetics are the greatest hazards. Mortality for exploratory thoracotomy ranges from 0.5 to 1.8%.

Transthoracic Needle Biopsy

Transthoracic needle biopsy of thoracic or mediastinal structures uses a cutting needle to aspirate a core of tissue for histologic analysis. Transthoracic needle biopsy is done to evaluate peripheral lung nodules or masses; hilar, mediastinal, and pleural abnormalities; and undiagnosed infiltrates or pneumonias when bronchoscopy is contraindicated or nondiagnostic. When done with the use of CT guidance and with a skilled cytopathologist in attendance, transthoracic needle biopsy confirms the diagnosis of cancer with > 95% accuracy. Needle biopsy yields an accurate diagnosis in benign processes only 50 to 60% of the time.

Contraindications: Contraindications are similar to those of thoracentesis. Additional contraindications include the following:

- Mechanical ventilation

- Contralateral pneumonectomy

- Suspected vascular lesions

- Putrid lung abscess

- Hydatid cyst

- Pulmonary hypertension

• Bullous lung disease

• Intractable coughing

• Coagulopathy, platelet count < 50,000/µL, and other bleeding diatheses

Procedure: Transthoracic needle biopsy is usually done by an interventional radiologist, often with a cytopathologist present. Under sterile conditions, local anesthesia, and imaging guidance—usually CT but sometimes ultrasonography for pleural-based lesions—a biopsy needle is passed into the suspected lesion while patients hold their breath. Lesions are aspirated with or without saline; 2 or 3 samples are collected for cytologic and bacteriologic processing. After the procedure, fluoroscopy and chest x-rays are used to rule out pneumothorax and hemorrhage. Core needle biopsies are used to obtain a cylinder of tissue suitable for histologic examination.

Complications: Complications include pneumothorax (10 to 37%), hemoptysis (10 to 25%), parenchymal hemorrhage, air embolism, and subcutaneous emphysema.

Tube Thoracostomy

Tube thoracostomy is insertion of a tube into the pleural space. It is used to drain air or fluid from the chest (eg, for large or recurrent effusion refractory to thoracentesis, pneumothorax, complicated parapneumonic effusions, empyema, or hemothorax) and to do pleurodesis or fibrinolytic adhesiolysis.

Procedure: Chest tube insertion is best done by a physician trained in the procedure. Other physicians can handle emergency situations (eg, tension pneumothorax) using a needle and syringe. Tube insertion requires 1 or 2 hemostats or Kelly clamps, a silk suture, gauze dressing, and a chest tube. Recommended tube sizes are 16 to 24 French (F) for pneumothorax; 20 to 24 F for malignant pleural effusion; 28 to 36 F for bronchopleural fistula, complicated parapneumonic effusions, and empyema; and 32 to 40 F for hemothorax.

The insertion site and patient position depend on whether air or fluid is being drained. For pneumothorax, the tube is usually inserted in the 4th intercostal space and for other indications in the 5th or 6th intercostal space, in the midaxillary line with the ipsilateral arm abducted above the head.

No specific patient preparation is necessary except, in some cases, conscious sedation. Under sterile conditions, the skin, subcutaneous tissue, rib periosteum, and parietal pleura are locally anesthetized, more generously than for thoracentesis (see p. 1864). Proper location is confirmed by return of air or fluid in the anesthetic syringe. A purse-string suture can be placed but not yet tied around the site while the anesthetic takes effect. A 2-cm skin incision is made, and the intercostal soft tissue down to the pleura is then bluntly dissected by advancing a clamped hemostat or Kelly clamp and opening it; the pleura is then perforated with the clamped instrument and opened in the same way. A finger can be used to widen the tract and confirm entry into the pleural space. The chest tube, with a clamp grasping the tip, is inserted through the tract and directed inferoposteriorly for effusions, or apically for pneumothorax, until all of the tube's holes are inside the chest wall. The pursestring suture is closed, the tube is sutured to the chest wall, and a sterile dressing with petroleum gauze to help seal the wound is placed over the site.

The tube is connected to water seal to prevent air from entering the chest through the tube and to allow drainage without suction (for effusions or empyema) or with suction (for pneumothorax). Posteroanterior and lateral chest x-rays are obtained after insertion to check the tube's position.

The tube is removed when the condition for which it was placed resolves. In the case of pneumothorax, suction is stopped and the tube is placed on water seal for several hours to ensure that the air leak has stopped and that the lung remains expanded. At the moment of removal, the patient is asked to take a deep breath and then to forcibly exhale; the tube is removed during exhalation and the site is covered with petroleum gauze, a sequence that reduces the chance of pneumothorax during removal. For effusions or hemothorax, the tube is typically removed when the drainage is < 100 mL/day.

Complications: Complications include the following:

- Malpositioning of the tube in the lung parenchyma, in the lobar fissure, under the diaphragm, or subcutaneously
- Clotting, kinking, or dislodgement of the tube, requiring replacement
- Re-expansion pulmonary edema
- Subcutaneous emphysema
- Infection of residual pleural fluid or recurrent effusion
- Pulmonary or diaphragmatic laceration
- Rarely perforation of other structures

Chest Physiotherapy

Chest physiotherapy consists of external mechanical maneuvers, such as chest percussion, postural drainage, and vibration, to augment mobilization and clearance of airway secretions. It is indicated for patients in whom cough is insufficient to clear thick, tenacious, or loculated secretions. Examples include patients with cystic fibrosis, bronchiectasis, lung abscess, neuromuscular disorders, and pneumonias in dependent lung regions.

Contraindications: Contraindications all are relative and include the following:

- Discomfort caused by physical positions or manipulations
- Anticoagulation
- Rib or vertebral fractures or osteoporosis
- Recent hemoptysis

Procedure: Chest physiotherapy may be administered by a respiratory therapist, although the techniques can often be taught to family members of patients.

The most common procedure used is postural drainage and chest percussion, in which the patient is rotated to facilitate drainage of secretions from a specific lobe or segment while being clapped with cupped hands to loosen and mobilize retained secretions that can then be expectorated or drained. The procedure is somewhat uncomfortable and tiring for the patient. Alternatives to chest percussion by hand include use of mechanical vibrators and inflatable vests.

Other methods that help clear airways include using controlled patterns of breathing, positive expiratory pressure devices to maintain airway patency, and ultra-low-frequency airway oscillation devices to mobilize sputum. The methods of airway clearance are comparable, and methods should be selected based on individual patient needs and preferences.

Complications: Complications are unusual but include position-related hypoxia and aspiration of secretions in other lung regions.

Pulmonary Rehabilitation

Pulmonary rehabilitation is the use of exercise, education, and behavioral intervention to enhance quality of life. It is indicated for any condition in which respiratory symptoms restrict activity (eg, COPD, interstitial lung disease, neuromuscular disorders causing chest wall weakness) and for respiratory retraining after prolonged ventilator dependence.

For many patients with chronic respiratory disorders, medical therapy only partially allays the symptoms and complications of the disorder. A comprehensive program of pulmonary rehabilitation may lead to significant clinical improvement by reducing shortness of breath, increasing exercise tolerance, and, to a lesser extent, decreasing the number of hospitalizations. However, these programs do not improve survival. There are no complications from pulmonary rehabilitation beyond those expected from physical exertion and exercise.

Contraindications: Contraindications are relative and include comorbidities that could complicate attempts to increase a patient's level of exercise (eg, untreated angina, left ventricular dysfunction). These comorbidities do not preclude application of other components of pulmonary rehabilitation programs, however.

Procedure: Pulmonary rehabilitation is best administered as part of an integrated program of exercise training, education, and psychosocial and behavioral intervention by a team of physicians, nurses, respiratory therapists, physical and occupational therapists, and psychologists or social workers.

Exercise training involves aerobic exercise and respiratory muscle and extremity strength training; lower extremity strength training may be particularly important for patients with COPD.

Education revolves around smoking cessation; teaching breathing strategies (such as pursed-lip breathing, in which exhalations are begun against closed lips to decrease respiratory rate, thereby decreasing gas trapping); principles of conserving physical energy; treatment options, including drug therapy; and advanced-care planning.

Psychosocial interventions involve counseling and feedback for the depression, anxieties, and fear that obstruct the patient's full participation in activities.

Chapter 191. Asthma

Introduction

Asthma is a disease of diffuse airway inflammation caused by a variety of triggering stimuli resulting in partially or completely reversible bronchoconstriction. Symptoms and signs include dyspnea, chest tightness, cough, and wheezing. The diagnosis is based on history, physical examination, and pulmonary function tests. Treatment involves controlling triggering factors and drug therapy, most commonly with inhaled β_2-agonists and inhaled corticosteroids. Prognosis is good with treatment.

Epidemiology

The prevalence of asthma has increased continuously since the 1970s, and it now affects an estimated 4 to 7% of people worldwide. More than 20 million people in the US are affected. Asthma is one of the most common chronic diseases of childhood, affecting more than 6 million children; it occurs more frequently in boys before puberty and in girls after puberty. It also occurs more frequently in blacks and Puerto Ricans. Despite its increasing prevalence, however, there has been a recent decline in mortality. About 4000 deaths occur from asthma annually in the US. However, the death rate is 5 times higher for blacks than for whites. Asthma is the leading cause of hospitalization for children and is the number one chronic condition causing elementary school absenteeism. In 2002, the total cost of asthma care was $14 billion.

Etiology

Development of asthma is multifactorial and depends on the interactions among multiple susceptibility genes and environmental factors.

Susceptibility genes are thought to include those for T-helper 1 and 2 (T_H1 and T_H2) cells, IgE, cytokines (IL-3, -4, -5, -9, and -13), granulocyte-monocyte colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), and the *ADAM33* gene, which may stimulate airway smooth muscle and fibroblast proliferation or regulate cytokine production.

Environmental factors may include the following:

• Allergen exposure

• Diet

• Perinatal factors

Evidence clearly implicates household allergens (eg, dust mite, cockroach, pets) and other environmental allergens in disease development in older children and adults. Diets low in vitamins C and E and in ω-3 fatty acids have been linked to asthma, as has obesity. Asthma has also been linked to perinatal factors, such as young maternal age, poor maternal nutrition, prematurity, low birthweight, and lack of breastfeeding.

On the other hand, endotoxin exposure early in life can induce tolerance and may be protective. Air pollution is not definitively linked to disease development, though it may trigger exacerbations. The role of childhood exposure to cigarette smoke is controversial, with some studies finding a contributory and some a protective effect.

Genetic and environmental components may interact by determining the balance between T_H1 and T_H2 cell lineages. Infants may be born with a predisposition toward proallergic and proinflammatory T_H2 immune responses, characterized by growth and activation of eosinophils and IgE production. Early childhood exposure to bacterial and viral infections and endotoxins may shift the body to T_H1 responses, which suppresses T_H2 cells and induces tolerance. Trends in developed countries toward smaller

families with fewer children, cleaner indoor environments, and early use of vaccinations and antibiotics may deprive children of these T_H2-suppressing, tolerance-inducing exposures and may partly explain the continuous increase in asthma prevalence in developed countries (the hygiene hypothesis).

Reactive airways dysfunction syndrome (RADS): Indoor exposures to nitrogen oxide and volatile organic compounds are implicated in the development of RADS, a persistent asthma-like syndrome in people with no history of asthma (see p. 1979). RADS appears to be distinct from asthma and may be, on occasion, a form of environmental lung disease. However, RADS and asthma have many clinical similarities (eg, wheezing, dyspnea, cough), and both may respond to corticosteroids.

Pathophysiology

Asthma involves

• Bronchoconstriction

• Airway edema and inflammation

• Airway hyperreactivity

• Airway remodeling

In patients with asthma, T_H2 cells and other cell types—notably, eosinophils and mast cells, but also other CD4+ subtypes and neutrophils—form an extensive inflammatory infiltrate in the airway epithelium and smooth muscle, leading to airway remodeling (ie, desquamation, subepithelial fibrosis, angiogenesis, smooth muscle hypertrophy). Hypertrophy of smooth muscle narrows the airways and increases reactivity to allergens, infections, irritants, parasympathetic stimulation (which causes release of pro-inflammatory neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide), and other triggers of bronchoconstriction. Additional contributors to airway hyperreactivity include loss of inhibitors of bronchoconstriction (epithelium-derived relaxing factor, prostaglandin E_2) and loss of other substances called endopeptidases that metabolize endogenous bronchoconstrictors. Mucus plugging and peripheral blood eosinophilia are additional classic findings in asthma and may be epiphenomena of airway inflammation.

Triggers: Common triggers of an asthma attack include

• Environmental and occupational allergens (numerous)

• Infections

• Exercise

• Inhaled irritants

• Emotion

• Aspirin

• Gastroesophageal reflux

Infectious triggers in young children include respiratory syncytial virus, rhinovirus, and parainfluenza virus infection. In older children and adults, URIs (particularly with rhinovirus) and pneumonia are common infectious triggers. Exercise can be a trigger, especially in cold or dry environments. Inhaled irritants, such as air pollution, cigarette smoke, perfumes, and cleaning products, are often involved. Emotions such as anxiety, anger, and excitement sometimes trigger attacks. Aspirin is a trigger in up to 30% of older patients and in patients with more severe asthma. Aspirin-induced asthma is typically accompanied by nasal polyps with nasal and sinus congestion. Gastroesophageal reflux disease (GERD) is a common

exacerbating factor among some patients with asthma, possibly via esophageal acid-induced reflex bronchoconstriction or by microaspiration of acid. Allergic rhinitis often coexists with asthma; it is unclear whether the two are different manifestations of the same allergic process or whether rhinitis is a discrete asthma trigger.

Response: In the presence of triggers, there is reversible airway narrowing and uneven lung ventilation. Relative perfusion exceeds relative ventilation in lung regions distal to narrowed airways; thus, alveolar O_2 tensions fall and alveolar CO_2 tensions rise. Most patients can compensate by hyperventilating, but in severe exacerbations, diffuse bronchoconstriction causes severe gas trapping, and the respiratory muscles are put at a marked mechanical disadvantage so that the work of breathing increases. Under these conditions, hypoxemia worsens and $PaCO_2$ rises. Respiratory and metabolic acidosis may result and, if left untreated, cause respiratory and cardiac arrest.

Classification

Unlike, eg, hypertension, in which one parameter (BP) defines the severity of the disorder and the efficacy of treatment, asthma causes a number of clinical and testing abnormalities. Also unlike most hypertension, asthma manifestations typically wax and wane. Thus, monitoring (and studying) asthma requires a consistent terminology and defined benchmarks.

Severity is the intrinsic intensity of the disease process (ie, how bad it is). Severity can usually be assessed directly only before treatment is started, because patients who have responded well to treatment by definition have few symptoms. Asthma severity is categorized as

• Intermittent

• Mild persistent

• Moderate persistent

• Severe persistent

The term status asthmaticus describes severe, intense, prolonged bronchospasm that is resistant to treatment.

Control is the degree to which symptoms, impairments, and risks are minimized by treatment. Control is the parameter assessed in patients receiving treatment. Good control is the goal of asthma management whatever the disease severity. Control is classified as

• Well controlled

• Not well controlled

• Very poorly controlled

Severity and control are assessed in terms of patient impairment and risk (see Table 191-1).

Impairment refers to the frequency and intensity of patients' symptoms and functional limitations. Impairment is assessed by spirometry, mainly forced expiratory volume in 1 sec (FEV_1), and the ratio of FEV_1 to forced vital capacity (FVC), as well as clinical features such as

• How often symptoms are experienced

• How often the patient awakens at night

• How often the patient uses a short-acting β_2-agonist for symptom relief

• How often asthma interferes with normal activity

Risk refers to the likelihood of future exacerbations or decline in lung function and the risk of adverse drug effects. Risk is assessed by long-term trends in spirometry and clinical features such as

• Frequency of need for oral corticosteroids

• Need for hospitalization

• Need for ICU admission

• Need for intubation

It is important to remember that the severity category does not predict how serious an exacerbation a patient may have. For example, a patient who has mild asthma with long periods of no or mild symptoms and normal pulmonary function may have a severe, life-threatening exacerbation.

Symptoms and Signs

Patients with mild asthma are typically asymptomatic between exacerbations. Patients with more severe disease and those with exacerbations experience dyspnea, chest tightness, audible wheezing, and coughing. Coughing may be the only symptom in some patients (cough-variant asthma). Symptoms can follow a circadian rhythm and worsen during sleep, often around 4 AM. Many patients with more severe disease waken during the night (nocturnal asthma).

Signs include wheezing, pulsus paradoxus (ie, a fall of systolic BP > 10 mm Hg during inspiration—see p. 2018), tachypnea, tachycardia, and visible efforts to breathe (use of neck and suprasternal [accessory] muscles, upright posture, pursed lips, inability to speak). The expiratory phase of respiration is prolonged, with an inspiratory:expiratory ratio of at least 1:3. Wheezes can be present through both phases or just on expiration, but patients with severe bronchoconstriction may have no audible wheezing because of markedly limited airflow.

Patients with a severe exacerbation and impending respiratory failure typically have some combination of altered consciousness, cyanosis, pulsus paradoxus > 15 mm Hg, O_2 saturation (O_{2sat}) < 90%, $PaCO_2$ > 45 mm Hg, or hyperinflation. Rarely, pneumothorax or pneumomediastinum is seen on chest x-ray.

Symptoms and signs disappear between acute attacks, although soft wheezes may be audible during forced expiration at rest, or after exercise in some asymptomatic patients. Hyperinflation of the lungs may alter the chest wall in patients with long-standing uncontrolled asthma, causing a barrel-shaped thorax.

All symptoms and signs are nonspecific, are reversible with timely treatment, and typically are brought on by exposure to one or more triggers.

Diagnosis

• Clinical evaluation

• Pulmonary function testing

Diagnosis is based on history and physical examination and is confirmed with pulmonary function tests. Diagnosis of causes and the exclusion of other disorders that cause wheezing are also important. Asthma and COPD are sometimes easily confused; they cause similar symptoms and produce similar results on pulmonary function tests but differ in important biologic ways that are not always clinically apparent.

Pulmonary function tests: Patients suspected of having asthma should undergo pulmonary

[Table 191-1. Classification of Asthma Control*†]

function testing to confirm and quantify the severity and reversibility of airway obstruction. Pulmonary function data quality is effort-dependent and requires patient education before the test. If it is safe to do so, bronchodilators should be stopped before the test: 6 h for short-acting β_2-agonists, such as albuterol; 8 h for ipratropium; 12 to 36 h for theophylline; 24 h for long-acting β_2-agonists, such as salmeterol and formoterol; and 48 h for tiotropium.

Spirometry (see Ch. 189) should be done before and after inhalation of a short-acting bronchodilator. Signs of airflow limitation before bronchodilator inhalation include reduced FEV_1 and a reduced FEV_1/FVC ratio. The FVC may also be decreased because of gas trapping, such that lung volume measurements may show an increase in the residual volume, the functional residual capacity, or both. An improvement in FEV_1 of > 12% or an increase ≥ 10% of predicted FEV_1 in response to bronchodilator treatment confirms reversible airway obstruction, although absence of this finding should not preclude a therapeutic trial of bronchodilators. Spirometry should be repeated at least every 1 to 2 yr in patients with asthma to monitor disease progression.

Flow-volume loops should also be reviewed to diagnose vocal cord dysfunction, a common cause of upper airway obstruction that mimics asthma.

Provocative testing, in which inhaled methacholine (or alternatives, such as inhaled histamine, adenosine, or bradykinin, or exercise testing) is used to provoke bronchoconstriction, is indicated for patients suspected of having asthma who have normal findings on spirometry and flow-volume testing, and for patients suspected of having cough-variant asthma, provided there are no contraindications. Contraindications include FEV_1 < 1 L or < 50%, recent MI or stroke, and severe hypertension (systolic BP > 200 mm Hg; diastolic BP > 100 mm Hg). A decline in FEV_1 of > 20% on provocative testing supports the diagnosis of asthma. However, FEV_1 may decline in response to these drugs in other disorders, such as COPD.

Other tests: Other tests may be helpful in some circumstances:

• Diffusing capacity for carbon monoxide (DLCO)

• Chest x-ray

• Allergy testing

DLCO testing can help distinguish asthma from COPD. Values are normal or elevated in asthma and usually reduced in COPD, particularly in patients with emphysema.

A chest x-ray may help exclude some causes of asthma or alternative diagnoses, such as heart failure or pneumonia. The chest x-ray in asthma is usually normal but may show hyperinflation or segmental atelectasis, a sign of mucous plugging. Infiltrates, especially those that come and go and that are associated with findings of central bronchiectasis, suggest allergic bronchopulmonary aspergillosis (see p. 1887).

Allergy testing may be indicated for children whose history suggests allergic triggers (particularly for allergic rhinitis) because these children may benefit from immunotherapy. It should be considered for adults whose history indicates relief of symptoms with allergen avoidance and for those in whom a trial of therapeutic anti-IgE antibody therapy (see p. 1881) is being considered. Skin testing and measurement of allergen-specific IgE via radioallergosorbent testing (RAST) can identify specific allergic triggers (see p. 1115).

Elevated blood eosinophils (> 400 cells/μL) and nonspecific IgE (> 150 IU) are suggestive but not diagnostic of allergic asthma because they can be elevated in other conditions.

Sputum evaluation for eosinophils is not commonly done; finding large numbers of eosinophils is suggestive of asthma but is neither sensitive nor specific.

Peak expiratory flow (PEF) measurements with inexpensive handheld flow meters are recommended for home monitoring of disease severity and for guiding therapy.

Evaluation of exacerbations: Patients with asthma with an acute exacerbation should have certain tests:

• Pulse oximetry

• PEF or FEV_1 measurement

All 3 measures help establish the severity of an exacerbation and document treatment response. PEF values are interpreted in light of the patient's personal best, which may vary widely among patients who are equally well controlled. A 15 to 20% reduction from this baseline indicates a significant exacerbation. When baseline values are not known, the percent predicted value gives a general idea of airflow limitation but not the individual patient's degree of worsening.

Chest x-ray is not necessary for most exacerbations but should be done in patients with symptoms suggestive of pneumonia or pneumothorax.

ABG measurements should be taken in patients with marked respiratory distress or symptoms and signs of impending respiratory failure.

Prognosis

Asthma resolves in many children, but for as many as 1 in 4, wheezing persists into adulthood or relapse occurs in later years. Female sex, smoking, earlier age of onset, sensitization to household dust mites, and airway hyperresponsiveness are risk factors for persistence and relapse.

About 4000 deaths/yr in the US are attributable to asthma, most of which are preventable with treatment. Thus, the prognosis is good with adequate access and adherence to treatment. Risk factors for death include increasing requirements for oral corticosteroids before hospitalization, previous hospitalization for acute exacerbations, and lower peak flow measurements at presentation. Several studies show that use of inhaled corticosteroids decreases hospital admission and mortality rates.

Over time, the airways in some patients with asthma undergo permanent structural changes (remodeling) that prevent return to normal lung functioning. Early aggressive use of anti-inflammatory drugs may help prevent this remodeling.

Treatment

• Control of triggers

• Drug therapy

• Monitoring

• Patient education

• Treatment of acute exacerbations

Treatment objectives are to minimize impairment and risk, including preventing exacerbations and minimizing chronic symptoms, including nocturnal awakenings; to minimize the need for emergency department visits or hospitalizations; to maintain baseline (normal) pulmonary function and activity levels; and to avoid adverse treatment effects.

Control of triggering factors: Triggering factors in some patients may be controlled with use of synthetic fiber pillows and impermeable mattress covers and frequent washing of bed sheets, pillowcases, and blankets in hot water. Upholstered furniture, soft toys, carpets, and pets should be removed (dust mites, animal dander). Dehumidifiers should be used in basements and in other poorly aerated, damp rooms (molds). Steam treatment of homes diminishes dust mite allergens. House cleaning and extermination to eliminate cockroach exposure is especially important. Although control of triggering factors is more difficult in urban environments, the importance of these measures is not diminished. High-efficiency particulate air (HEPA) vacuums and filters may relieve symptoms, but beneficial effects on pulmonary function and on the need for drugs are unproved. Sulfite-sensitive patients should avoid red wine. Nonallergenic triggers, such as cigarette smoke, strong odors, irritant fumes, cold temperatures, high humidity, and exercise, should also be avoided or controlled when possible. Avoidance of viral URIs is also important. Patients with aspirin-induced asthma can use acetaminophen, choline magnesium salicylate, or selective cyclooxygenase-2 (COX-2) inhibitors in place of NSAIDs. Asthma is a relative contraindication to the use of nonselective β-blockers, including topical formulations, but cardioselective drugs (eg, metoprolol, atenolol) probably have no adverse effects.

Drug therapy: Major drug classes commonly used in the treatment of chronic asthma and asthma exacerbations include

• Bronchodilators (β_2-agonists, anticholinergics)

• Corticosteroids

• Leukotriene modifiers

• Mast cell stabilizers

• Methylxanthines

Drugs in these classes (see Table 191-2) are inhaled or taken orally; inhaled drugs come in aerosolized and powdered forms. Use of aerosolized forms with a spacer or holding chamber facilitates deposition of the drug in the airways rather than the pharynx; patients are advised to wash and dry their spacers after each use to prevent bacterial contamination. In addition, use of aerosolized forms requires coordination between actuation of the inhaler (drug delivery) and inhalation; powdered forms reduce the need for coordination, because drug is delivered only when the patient inhales. In addition, powdered forms reduce the release of fluorocarbon propellants into the environment.

β_2-Agonists relax bronchial smooth muscle, decrease mast cell degranulation and histamine release, inhibit microvascular leakage into the airways, and increase mucociliary clearance. β_2-Agonists come in short- and long-acting preparations (see Table 191-2). Short-acting β_2-agonists (eg, albuterol) 2 puffs inhaled q 4 h prn are the drug of choice for relieving acute bronchoconstriction and preventing exercise-induced asthma. They are not used for long-term maintenance. They take effect within minutes and are active for up to 6 to 8 h, depending on the drug. Tachycardia and tremor are the most common acute adverse effects of inhaled β_2-agonists and are dose-related. Mild hypokalemia occurs uncommonly. Use of levalbuterol (a solution containing the *R*-isomer of albuterol) theoretically minimizes adverse effects, but its long-term efficacy and safety are unproved. Oral β_2-agonists have more systemic effects and generally should be avoided.

Long-acting β_2-agonists (eg, salmeterol) are active for up to 12 h and are used for moderate and severe asthma but should never be used as monotherapy. They interact synergistically with inhaled corticosteroids and permit lower dosing of corticosteroids. The safety of regular long-term use of β_2-agonists is controversial. Long-acting β_2-agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, salmeterol should be used only as additional therapy, not monotherapy, for patients whose condition is not adequately controlled with other asthma controllers (eg, low- to mediumdose inhaled corticosteroids) or whose disease severity clearly warrants additional

maintenance therapies. Daily use of β_2-agonists, increased dosing or diminishing effects, or use of ≥ 1 canisters a month suggests inadequate control and the need to begin or intensify other therapies.

[**Table 191-2.** Drug Treatment of Chronic Asthma*]

Anticholinergics relax bronchial smooth muscle through competitive inhibition of muscarinic (M_3) cholinergic receptors. Ipratropium may have an additive effect when combined with short-acting β_2-agonists. Adverse effects include pupillary dilation, blurred vision, and dry mouth. Tiotropium is a 24-h inhaled anticholinergic that has not been adequately evaluated for asthma use.

Corticosteroids inhibit airway inflammation, reverse β-receptor down-regulation, and inhibit cytokine production and adhesion protein activation. They block the late response (but not the early response) to inhaled allergens. Routes of administration include oral, IV, and inhaled. In acute asthma exacerbation, early use of systemic corticosteroids often aborts the exacerbation, decreases the need for hospitalization, prevents relapse, and speeds recovery. Oral and IV routes are equally effective. Inhaled corticosteroids have no role in acute exacerbation but are indicated for long-term suppression, control, and reversal of inflammation and symptoms. They substantially reduce the need for maintenance oral corticosteroid therapy. Adverse local effects of inhaled corticosteroids include dysphonia and oral candidiasis, which can be prevented or minimized by having the patient use a spacer, gargle with water after corticosteroid inhalation, or both. Systemic effects are all dose-related, can occur with oral or inhaled forms, and occur mainly with inhaled doses > 800 µg/day. They include suppression of the adrenal-pituitary axis, osteoporosis, cataracts, skin atrophy, hyperphagia, and easy bruisability. Whether inhaled corticosteroids suppress growth in children is controversial: Most children reach their predicted adult height. Latent TB may be reactivated by systemic corticosteroid use.

Mast cell stabilizers inhibit histamine release from mast cells, reduce airway hyperresponsiveness, and block the early and late responses to allergens. They are given by inhalation prophylactically to patients with exercise-induced or allergen-induced asthma. They are ineffective once symptoms have occurred. They are the safest of all antiasthmatic drugs but the least effective.

Leukotriene modifiers are taken orally and can be used for long-term control and prevention of symptoms in patients with mild persistent to severe persistent asthma. The main adverse effect is liver enzyme elevation (which occurs with zileuton). Although rare, patients have developed a clinical syndrome resembling that of Churg-Strauss syndrome.

Methylxanthines relax bronchial smooth muscle (probably by inhibiting phosphodiesterase) and may improve myocardial and diaphragmatic contractility through unknown mechanisms. Methylxanthines appear to inhibit intracellular release of Ca, decrease microvascular leakage into the airway mucosa, and inhibit the late response to allergens. They decrease the infiltration of eosinophils into bronchial mucosa and of T lymphocytes into epithelium. Methylxanthines are used for long-term control as an adjunct to β_2-agonists; extended-release theophylline helps manage nocturnal asthma. Theophylline is falling into disuse because of its many adverse effects and interactions compared with other drugs. Adverse effects include headache, vomiting, cardiac arrhythmias, and seizures. Methylxanthines have a narrow therapeutic index; multiple drugs (any metabolized by the cytochrome P-450 pathway, eg, macrolide antibiotics) and conditions (eg, fever, liver disease, heart failure) alter methylxanthine metabolism and elimination. Serum theophylline levels should be monitored periodically and maintained between 5 and 15 µg/mL (28 and 83 µmol/L).

Immunomodulators include omalizumab, an anti-IgE antibody developed for use in severely allergic patients with asthma who have elevated IgE levels. Omalizumab may decrease asthma exacerbations, decreases corticosteroid requirements, and relieves symptoms. Dosing is determined by a dosing chart based on the patient's weight and IgE levels. The drug is administered sc q 2 to 4 wk. Clinicians who administer omalizumab should be prepared to identify and treat anaphylaxis, which may occur.

Other drugs are used uncommonly in specific circumstances. Magnesium is often used in the emergency department, but it is not recommended in the management of chronic asthma. Immunotherapy may be indicated when symptoms are triggered by allergy, as suggested by history and confirmed by allergy

testing. Immunotherapy is generally more effective in children than adults. If symptoms are not significantly relieved after 24 mo, then therapy is stopped. If symptoms are relieved, therapy should continue for ≥ 3 yr, although the optimum duration is unknown. Other drugs that suppress the immune system are occasionally prescribed to reduce dependence on high-dose oral corticosteroids, but these drugs have a significant risk of toxicity. Low-dose methotrexate (5 to 15 mg once/wk) can lead to modest improvements in FEV_1 and modest decreases in daily oral corticosteroid use. Gold and cyclosporine are also modestly effective, but toxicity and need for monitoring limit their use. Other therapies for management of chronic asthma include nebulized lidocaine, nebulized heparin, colchicine, and high-dose IV immune globulin. Limited evidence supports the use of any of these therapies, and their benefits are unproved, so none are currently recommended for routine clinical use.

Monitoring response to treatment: Guidelines recommend office use of spirometry (FEV_1, FEV_1/FVC, FVC) to measure airflow limitation and assess impairment and risk. Outside the office, home PEF monitoring, in conjunction with patient symptom diaries and the use of an asthma action plan, is especially useful for charting disease progression and response to treatment in patients with moderate to severe persistent asthma. When asthma is quiescent, one PEF measurement in the morning suffices. Should PEF measurements fall to < 80% of the patient's personal best, then twice/day monitoring to assess circadian variation is useful. Circadian variation of > 20% indicates airway instability and the need to re-evaluate the therapeutic regimen.

Patient education: The importance of patient education cannot be overemphasized. Patients do better when they know more about asthma—what triggers an attack, what drug to use when, proper inhaler technique, how to use a spacer with a metered-dose inhaler (MDI), and the importance of early use of corticosteroids in exacerbations. Every patient should have a written action plan for day-to-day management, especially for management of acute attacks, that is based on the patient's best personal peak flow rather than on a predicted normal value. Such a plan leads to much better asthma control, largely attributable to improved adherence to therapies.

Treatment of acute exacerbation: The goal of asthma exacerbation treatment is to relieve symptoms and return patients to their best lung function. Treatment includes

• Inhaled bronchodilators (β_2-agonists and anticholinergics)

• Usually systemic corticosteroids

Patients having an attack are instructed to self-administer 2 to 4 puffs of inhaled albuterol or a similar short-acting β_2-agonist up to 3 times spaced 20 min apart for an acute exacerbation and to measure PEF if possible. When these short-acting rescue drugs are effective (symptoms are relieved and PEF returns to > 80% of baseline), the acute exacerbation may be managed in the outpatient setting. Patients who do not respond, have severe symptoms, or have a PEF persistently < 80% should follow a treatment management program outlined by the physician or should go to the emergency department (see Table 191-3 for specific dosing information).

Inhaled bronchodilators (β_2-agonists and anticholinergics) are the mainstay of asthma

[**Table 191-3.** Drug Treatment of Asthma Exacerbations*]

treatment in the emergency department. In adults and older children, albuterol given by an MDI and spacer is as effective as that given by nebulizer. Nebulized treatment is preferred for younger children because of difficulties coordinating MDIs and spacers; evidence suggests that bronchodilator response improves when the nebulizer is powered with helium-O_2 (heliox) rather than with O_2. Subcutaneous epinephrine 1:1000 solution or terbutaline is an alternative for children. Terbutaline may be preferable to epinephrine because of its lesser cardiovascular effects and longer duration of action, but it is no longer produced in large quantities and is expensive. Subcutaneous administration of β_2-agonists in adults raises concerns of adverse cardiostimulatory effects. However, clinically important adverse effects are few, and subcutaneous administration may benefit patients unresponsive to maximal inhaled therapy or patients unable to receive effective nebulized treatment (eg, those who cough excessively, have poor

ventilation, or are uncooperative). Nebulized ipratropium can be co-administered with nebulized albuterol for patients who do not respond optimally to albuterol alone; some evidence favors simultaneous high-dose β_2-agonist and ipratropium as first-line treatment, but no data favor continuous β_2-agonist nebulization over intermittent administration. Theophylline has very little role in treatment.

Systemic corticosteroids (prednisone, prednisolone, methylprednisolone) should be given for all but the mildest acute exacerbation; they are unnecessary for patients whose PEF normalizes after 1 or 2 bronchodilator doses. IV and oral routes of administration are probably equally effective. IV methylprednisolone can be given if an IV line is already in place and can be switched to oral dosing whenever necessary or convenient. Tapering usually starts after 7 to 10 days and should last 2 to 3 wk.

Antibiotics are indicated only when history, examination, or chest x-ray suggests underlying bacterial infection; most infections underlying asthma exacerbations are probably viral in origin.

Supplemental O_2 is indicated for hypoxemia and should be given by nasal cannula or face mask at a flow rate or concentration sufficient to maintain O_{2sat} > 90%.

Reassurance is the best approach when anxiety is the cause of asthma exacerbation. Anxiolytics and morphine are relatively contraindicated because they are associated with increased mortality and the need for mechanical ventilation.

Hospitalization generally is required if patients have not returned to their baseline within 4 h of aggressive emergency department treatment. Criteria for hospitalization vary, but definite indications are failure to improve, worsening fatigue, relapse after repeated β_2-agonist therapy, and significant decrease in PaO_2 (< 50 mm Hg) or increase in $PaCO_2$ (> 40 mm Hg), indicating progression to respiratory failure.

Patients who continue to deteriorate despite aggressive treatment are candidates for noninvasive positive pressure ventilation or endotracheal intubation and invasive mechanical ventilation (see p. 2279). Patients requiring intubation may benefit from sedation, but neuromuscular blocking agents should be avoided because of possible interactions with corticosteroids that can cause prolonged neuromuscular weakness.

Generally, volume-cycled ventilation in assist-control mode is used because it provides constant alveolar ventilation when airway resistance is high and changing. The ventilator should be set to a relatively low frequency with a relatively high inspiratory flow rate (> 80 L/min) to prolong exhalation time, minimizing autopositive end-expiratory pressure (PEEP). Initial tidal volumes can be set to 6 to 10 mL/kg. High peak airway pressures can generally be ignored, because they result from high airway resistance and inspiratory flow rates and do not reflect the degree of lung distention caused by alveolar pressure. However, if plateau pressures exceed 30 to 35 cm H_2O, then tidal volume should be reduced to limit the risk of pneumothorax. When reduced tidal volumes are necessary, a moderate degree of hypercapnia is acceptable, but if arterial pH falls below 7.10, a slow $NaHCO_3$ infusion is indicated to maintain pH between 7.20 and 7.25. Once airflow obstruction is relieved and $PaCO_2$ and arterial pH normalize, patients can usually be quickly weaned from the ventilator.

Other therapies are reportedly effective for asthma exacerbation, but none have been thoroughly studied. Heliox is used to decrease the work of breathing and improve ventilation through a decrease in turbulent flow attributable to helium, a gas less dense than O_2. Despite the theoretical benefits of heliox, studies have reported conflicting results concerning its efficacy; lack of ready availability also limits its use. Magnesium sulfate relaxes smooth muscle, but efficacy in management of asthma exacerbation in the emergency department is debated. General anesthesia in patients with status asthmaticus causes bronchodilation by an unclear mechanism, perhaps by a direct relaxant effect on airway smooth muscle or attenuation of cholinergic tone.

Treatment of chronic asthma: Current asthma guidelines initiate treatment based on the severity classification. Continuing therapy is based on assessment of control (see Table 191-1). Therapy is increased in a stepwise fashion (see

Table 191-4) until the best control of impairment and risk is achieved (step-up). Before therapy is stepped up, adherence, exposure to environmental factors (eg, trigger exposure), and presence of comorbid conditions (eg, obesity, allergic rhinitis, gastroesophageal reflux disease, COPD, obstructive sleep apnea, vocal cord dysfunction) are reviewed. These factors should be addressed before increasing drug therapy. Once asthma has been well controlled for at least 3 mo, drug therapy is reduced if possible to the minimum that maintains good control (step-down). For specific drugs and doses, see Table 191-2.

Exercise-induced asthma: Exercise-induced asthma can generally be prevented by inhalation of a short-acting β_2-agonist or mast cell stabilizer before starting the exercise. If β_2-agonists are not effective or if exercise-induced asthma is associated with severe symptoms, the patient has more severe asthma than is recognized and requires controller therapy.

[**Table 191-4.** Steps of Asthma Management*]

Aspirin-sensitive asthma: The primary treatment for aspirin-sensitive asthma is avoidance of NSAIDs. Cyclooxygenase-2 (COX-2) inhibitors do not appear to be triggers. Leukotriene modifiers can blunt the response to NSAIDs. Alternatively, inpatient desensitization has been successful in a few patients.

Future therapies: Multiple therapies are being developed to target specific components of the inflammatory cascade. Therapies directed at IL-4, IL-13, tumor necrosis factor-α, other chemokines, and cytokines or their receptors are all under investigation or consideration as therapeutic targets.

Special Populations

Infants, children, and adolescents: Asthma is difficult to diagnose in infants; thus, under-recognition and undertreatment are common. Empiric trials of inhaled bronchodilators and anti-inflammatory drugs may be helpful for both. Drugs may be given by nebulizer or MDI with a holding chamber with or without a face mask. Infants and children < 5 yr requiring treatment > 2 times/wk should be given daily anti-inflammatory therapy with inhaled corticosteroids (preferred), leukotriene receptor antagonists, or cromolyn.

Children > 5 yr and adolescents with asthma can be treated similarly to adults but should be encouraged to maintain physical activities, exercise, and sports participation. Predicted norms for pulmonary function tests in adolescents are closer to childhood (not adult) standards. Adolescents and mature younger children should participate in developing their own asthma management plans and establishing their own goals for therapy to improve adherence. The action plan should be understood by teachers and school nurses to ensure reliable and prompt access to rescue drugs. Cromolyn and nedocromil are often tried in this group but are not as beneficial as inhaled corticosteroids. Long-acting drugs prevent the embarrassment of having to take drugs at school.

Pregnant women: About one third of women with asthma who become pregnant notice relief of symptoms, one third notice worsening (at times to a severe degree), and one third notice no change. GERD may be an important contributor to symptomatic disease in pregnancy. Asthma control during pregnancy is crucial (see p. 2636), because poorly controlled maternal disease can result in increased prenatal mortality, premature delivery, and low birth weight. Asthma drugs have not been shown to have adverse fetal effects, but safety data are lacking.

Elderly patients: The elderly have a high prevalence of other obstructive lung disease (eg, COPD), so it is important to determine the magnitude of the reversible component of airflow obstruction (eg, by a 2- to 3-wk trial of inhaled corticosteroids or pulmonary function testing with bronchodilator challenge). The elderly may be more sensitive to adverse effects of β_2-agonists and inhaled corticosteroids. Patients requiring inhaled corticosteroids, particularly those with risk factors for osteoporosis, may benefit from measures to preserve bone density (eg, Ca and vitamin D supplements, bisphosphonates).

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to *Aspergillus fumigatus* that occurs almost exclusively in patients with asthma or, less commonly, cystic

fibrosis. Immune responses to *Aspergillus* antigens cause airway obstruction and, if untreated, bronchiectasis and pulmonary fibrosis. Symptoms and signs are those of asthma with the addition of productive cough and, occasionally, fever and anorexia. Diagnosis is suspected based on history and imaging tests and confirmed by *Aspergillus* skin testing and measurement of IgE levels, circulating precipitins, and *A. fumigatus*-specific antibodies. Treatment is with corticosteroids and, in patients with refractory disease, itraconazole.

ABPA develops when airways of patients with asthma or cystic fibrosis become colonized with *Aspergillus* sp (ubiquitous fungi in the soil).

Pathophysiology

For unclear reasons, colonization in these patients prompts vigorous antibody (IgE and IgG) and cell-mediated immune responses (type I, III, and IV hypersensitivity reactions) to *Aspergillus* antigens, leading to frequent, recurrent asthma exacerbations. Over time, the immune reactions, combined with direct toxic effects of the fungus, lead to airway damage with dilatation and, ultimately, bronchiectasis and fibrosis. The disorder is characterized histologically by mucoid impaction of airways, eosinophilic pneumonia, infiltration of alveolar septa with plasma and mononuclear cells, and an increase in the number of bronchiolar mucous glands and goblet cells. Rarely, other fungi, such as *Penicillium*, *Candida*, *Curvularia*, *Helminthosporium*, and *Drechslera* spp, cause an identical syndrome called allergic bronchopulmonary mycosis in the absence of underlying asthma or cystic fibrosis.

Aspergillus is present intraluminally but is not invasive. Thus, ABPA must be distinguished from invasive aspergillosis, which occurs in immunocompromised patients; from aspergillomas, which are collections of *Aspergillus* in patients with established cavitary lesions or cystic airspaces; and from the rare *Aspergillus* pneumonia, which occurs in patients who take low doses of prednisone long term (eg, patients with COPD).

Symptoms and Signs

Symptoms are those of asthma or pulmonary cystic fibrosis exacerbation, with the addition of cough productive of dirty-green or brown plugs and, occasionally, hemoptysis. Fever, headache, and anorexia are common systemic symptoms in severe disease. Signs are those of airway obstruction, specifically, wheezing and prolonged expiration, which are indistinguishable from asthma exacerbation.

Diagnosis

• History of asthma

• Chest x-ray or high-resolution CT

• Skin prick test with *Aspergillus* antigen

• *Aspergillus* precipitins in blood

• IgE levels

The diagnosis is suspected in patients with asthma with recurrent asthma exacerbations, migratory or nonresolving infiltrates on chest x-ray (often due to atelectasis from mucoid plugging and bronchial obstruction), evidence of bronchiectasis on imaging studies (see p. 1941), sputum cultures positive for *A. fumigatus*, or notable peripheral eosinophilia.

Several criteria have been proposed for the diagnosis (see Table 191-5), but in practice 4 essential criteria are generally assessed. An immediate wheal-and-flare reaction to an initial skin prick test with *Aspergillus* antigen should prompt measurement of serum IgE and *Aspergillus* precipitins; up to 25% of patients with asthma without ABPA may have a positive skin test. An IgE level > 1000 ng/mL and positive precipitins suggest the diagnosis, which should be confirmed by

measurement of specific anti-*Aspergillus* immunoglobulins (up to 10% of healthy patients have circulating precipitins). A finding of *A. fumigatus*-specific IgG and IgE antibodies in concentrations at least twice those found in patients without ABPA establishes the diagnosis. Whenever test results diverge, such as with an IgE > 1000 ng/mL but negative *A. fumigatus*-specific immunoglobulins, testing should be repeated, the patient should be monitored over time to definitively establish or exclude the diagnosis.

Treatment

• Prednisone

• Sometimes antifungal drugs

[**Table 191-5.** Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis]

[
Table 191-6. Stages of Allergic Bronchopulmonary Aspergillosis*]

Treatment is based on disease stage (see Table 191-6). Stage I is treated with prednisone 0.5 to 0.75 mg/kg once/day for 2 to 4 wk, then tapered over 4 to 6 mo. Chest x-ray, blood eosinophils, and IgE levels should be checked quarterly for improvement, defined as resolution of infiltrates, ≥ 50% decline in eosinophils, and 33% decline in IgE. Patients who achieve stage II disease require annual monitoring only. Stage II patients who relapse (Stage III) are given another trial of prednisone. Stage I or III patients who do not improve with prednisone (Stage IV) are candidates for antifungal treatment. Itraconazole 200 mg po bid for 4 to 6 mo with a 6-mo taper is recommended as a substitute for prednisone and as a corticosteroid-sparing drug. Itraconazole therapy requires checking drug levels and monitoring liver enzymes and triglyceride and potassium levels.

All patients should be optimally treated for their underlying asthma or cystic fibrosis. In addition, patients taking long-term corticosteroids should be monitored for complications, such as cataracts, hyperglycemia, and osteoporosis, and possibly prescribed treatments to prevent bone demineralization and *Pneumocystis jirovecii* lung infection.

Chapter 192. Chronic Obstructive Pulmonary Disease

Introduction

Chronic obstructive pulmonary disease (COPD) is partially reversible airflow limitation caused by an inflammatory response to inhaled toxins, often cigarette smoke. α_1-Antitrypsin deficiency and various occupational exposures are less common causes in nonsmokers. Symptoms are productive cough and dyspnea that develop over years; common signs include decreased breath sounds, prolonged expiratory phase of respiration, and wheezing. Severe cases may be complicated by weight loss, pneumothorax, frequent acute decompensation episodes, right heart failure, and acute or chronic respiratory failure. Diagnosis is based on history, physical examination, chest x-ray, and pulmonary function tests. Treatment is with bronchodilators, corticosteroids, and, when necessary, O_2 and antibiotics. About 50% of patients die within 10 yr of diagnosis.

COPD comprises

• Chronic obstructive bronchitis (clinically defined)

• Emphysema (pathologically or radiologically defined)

Many patients have features of both.

Chronic obstructive bronchitis is chronic bronchitis with airflow obstruction. Chronic bronchitis is defined as productive cough on most days of the week for at least 3 mo total duration in 2 successive years. Chronic bronchitis becomes chronic obstructive bronchitis if spirometric evidence of airflow obstruction develops. Chronic asthmatic bronchitis is a similar, overlapping condition characterized by chronic productive cough, wheezing, and partially reversible airflow obstruction; it occurs predominantly in smokers with a history of asthma. In some cases, the distinction between chronic obstructive bronchitis and chronic asthmatic bronchitis is unclear.

Emphysema is destruction of lung parenchyma leading to loss of elastic recoil and loss of alveolar septa and radial airway traction, which increases the tendency for airway collapse. Lung hyperinflation, airflow limitation, and air trapping follow. Airspaces enlarge and may eventually develop bullae.

Epidemiology

An estimated 24 million people in the US have airflow limitation, of whom about half have COPD. COPD is the 4th leading cause of death, resulting in 122,000 deaths in 2003—compared with 52,193 deaths in 1980. From 1980 to 2000, the COPD mortality rate increased 64% (from 40.7 to 66.9/100,000). Prevalence, incidence, and mortality rates increase with age. Prevalence is higher in men, but total mortality is similar in both sexes. Incidence and mortality are generally higher in whites, blue-collar workers, and people with fewer years of formal education, probably because these groups have a higher prevalence of smoking. COPD seems to aggregate in families independent of α_1-antitrypsin (α_1-antiprotease inhibitor) deficiency (see p. 1901).

COPD is increasing worldwide because of the increase in smoking in developing countries, the reduction in mortality due to infectious diseases, and the widespread use of biomass fuels. It caused an estimated 2.74 million deaths worldwide in the year 2000 and is projected to become one of the top 5 causes of disease burden globally by the year 2020.

Etiology

There are several causes of COPD:

• Smoking (and less often other inhalational exposures)

• Genetic factors

Inhalational exposure: Of all inhalational exposures, cigarette smoking is the primary risk factor in most countries, although only about 15% of smokers develop clinically apparent COPD; an exposure history of 40 or more pack-years is especially predictive. Smoke from burning biomass fuels for indoor cooking and heating is an important contributing factor in developing countries. Smokers with preexisting airway reactivity (defined by increased sensitivity to inhaled methacholine), even in the absence of clinical asthma, are at greater risk of developing COPD than are those without.

Low body weight, childhood respiratory disorders, and exposure to passive cigarette smoke, air pollution, and occupational dust (eg, mineral dust, cotton dust) or inhaled chemicals (eg, cadmium) contribute to the risk of COPD but are of minor importance compared with cigarette smoking.

Genetic factors: The best-defined causative genetic disorder is α_1-antitrypsin deficiency (see p. 1901), which is an important cause of emphysema in nonsmokers and influences susceptibility to disease in smokers.

Polymorphisms in microsomal epoxide hydrolase, vitamin D-binding protein, IL-1β, IL-1 receptor antagonist, phospholipase A_2, matrix metalloproteinase 9, and *ADAM-33* genes are all associated with rapid decline in forced expiratory volume in 1 sec (FEV_1) in selected populations.

Pathophysiology

Various factors cause the airflow limitation and other complications of COPD.

Inflammation: Inhalational exposures can trigger an inflammatory response in airways and alveoli that leads to disease in genetically susceptible people. The process is thought to be mediated by an increase in protease activity and a decrease in antiprotease activity (see p. 1901). Lung proteases, such as neutrophil elastase, matrix metalloproteinases, and cathepsins, break down elastin and connective tissue in the normal process of tissue repair. Their activity is normally balanced by antiproteases, such as α_1-antitrypsin, airway epithelium-derived secretory leukoproteinase inhibitor, elafin, and matrix metalloproteinase tissue inhibitor. In patients with COPD, activated neutrophils and other inflammatory cells release proteases as part of the inflammatory process; protease activity exceeds antiprotease activity, and tissue destruction and mucus hypersecretion result. Neutrophil and macrophage activation also leads to accumulation of free radicals, superoxide anions, and hydrogen peroxide, which inhibit antiproteases and cause bronchoconstriction, mucosal edema, and mucous hypersecretion. Neutrophilinduced oxidative damage, release of profibrotic neuropeptides (eg, bombesin), and reduced levels of vascular endothelial growth factor may contribute to apoptotic destruction of lung parenchyma.

The inflammation in COPD increases with increasing disease severity, and, in severe (advanced) disease, inflammation does not resolve completely with smoking cessation. This inflammation does not seem to respond to corticosteroids.

Infection: Respiratory infection (which COPD patients are prone to), in conjunction with cigarette smoking, may amplify progression of lung destruction.

Bacteria, especially *Haemophilus influenzae*, colonize the normally sterile lower airways of about 30% of patients with COPD. In more severely affected patients (eg, those with previous hospitalizations), *Pseudomonas aeruginosa* colonization is common. Smoking and airflow obstruction may lead to impaired mucus clearance in lower airways, which predisposes to infection. Repeated bouts of infection increase the inflammatory burden that hastens disease progression. There is no evidence, however, that long-term use of antibiotics slows the progression of COPD.

Airflow limitation: The cardinal pathophysiologic feature of COPD is airflow limitation caused by airway obstruction, loss of elastic recoil, or both.

Airway obstruction is caused by inflammation-mediated mucus hypersecretion, mucus plugging, mucosal

edema, bronchospasm, peribronchial fibrosis, or a combination of these mechanisms. Alveolar attachments and alveolar septa are destroyed, contributing to loss of airway support and airway closure during expiration.

Enlarged alveolar spaces sometimes consolidate into bullae, defined as airspaces ≥ 1 cm in diameter. Bullae may be entirely empty or have strands of lung tissue traversing them in areas of locally severe emphysema; they occasionally occupy the entire hemithorax. These changes lead to loss of elastic recoil and lung hyperinflation.

Increased airway resistance increases the work of breathing, as does lung hyperinflation. Increased work of breathing may lead to alveolar hypoventilation with hypoxia and hypercapnia, although hypoxia is also caused by ventilation/perfusion (V/Q) mismatch.

Complications: In addition to airflow limitation and sometimes respiratory insufficiency, complications include

• Pulmonary hypertension

• Respiratory infection

• Weight loss and other comorbidities

Chronic hypoxemia increases pulmonary vascular tone, which, if diffuse, causes pulmonary hypertension (see p. 1984) and cor pulmonale (see p. 2132).

Viral or bacterial respiratory infections are common among patients with COPD and cause a large percentage of acute exacerbations. It is currently thought that acute bacterial infections are due to acquisition of new strains of bacteria rather than overgrowth of chronic colonizing bacteria.

Weight loss may occur, perhaps in response to decreased caloric intake and increased levels of circulating tumor necrosis factor (TNF)-α.

Other coexisting or complicating disorders that adversely affect quality of life and survival include osteoporosis, depression, coronary artery disease, lung cancer, muscle atrophy, and gastroesophageal reflux. The extent to which these disorders are consequences of COPD, smoking, and the accompanying systemic inflammation is unclear.

Symptoms and Signs

COPD takes years to develop and progress. Most patients have smoked ≥ 20 cigarettes/day for > 20 yr. Productive cough usually is the initial symptom, developing among smokers in their 40s and 50s. Dyspnea that is progressive, persistent, exertional, or worse during respiratory infection appears when patients are in their late 50s or 60s. Symptoms usually progress quickly in patients who continue to smoke and in those who have a higher lifetime tobacco exposure. Morning headache develops in more advanced disease and signals nocturnal hypercapnia or hypoxemia.

Acute exacerbations occur sporadically during the course of COPD and are heralded by increased symptom severity. The specific cause of any exacerbation is almost always impossible to determine, but exacerbations are often attributed to viral URIs or acute bacterial bronchitis. As COPD progresses, acute exacerbations tend to become more frequent, averaging about 3 episodes/yr.

Signs of COPD include wheezing, increased expiratory phase of breathing, lung hyperinflation manifested as decreased heart and lung sounds, and increased anteroposterior diameter of the thorax (barrel chest). Patients with advanced emphysema lose weight and experience muscle wasting that has been attributed to immobility, hypoxia, or release of systemic inflammatory mediators, such as TNF-α. Signs of advanced disease include pursed-lip breathing, accessory muscle use, paradoxical inward movement of the lower intercostal interspaces during inspiration (Hoover's sign), and cyanosis. Signs of cor pulmonale include neck vein distention, splitting of the 2nd heart sound with an accentuated pulmonic component, tricuspid

insufficiency murmur, and peripheral edema. Right ventricular heaves are uncommon in COPD because the lungs are hyperinflated.

Spontaneous pneumothorax may occur as a result of rupture of bullae and should be suspected in any patient with COPD whose pulmonary status abruptly worsens.

Diagnosis

• Chest x-ray

• Pulmonary function testing

Diagnosis is suggested by history, physical examination, and chest imaging and is confirmed by pulmonary function tests. Differential diagnosis includes asthma, heart failure, and bronchiectasis. COPD and asthma are sometimes easily confused. Asthma (see also p. 1868) and COPD are distinguished by numerous factors (see Table 192-1).

Systemic disorders that may have a component of airflow limitation may suggest COPD; they include HIV infection, abuse of IV drugs (particularly cocaine and amphetamines), sarcoidosis, Sjogren's syndrome, bronchiolitis obliterans, lymphangioleiomyomatosis, and eosinophilic granuloma.

Pulmonary function tests: Patients suspected of having COPD should undergo complete pulmonary function testing (see also p. 1851) to confirm airflow limitation, to quantify its severity and reversibility, and to distinguish COPD from other disorders. Pulmonary function testing is also useful for following disease progression and monitoring response to treatment. The primary diagnostic tests are

• FEV_1, which is the volume of air forcefully expired during the first second after taking a full breath

• Forced vital capacity (FVC), which is the total volume of air expired with maximal force

• Flow-volume loops, which are simultaneous spirometric recordings of airflow and volume during forced maximal expiration and inspiration

Reductions of FEV_1, FVC, and the ratio of FEV_1/FVC are the hallmark of airflow limitation. Flow-volume loops show a concave pattern in the expiratory tracing (see Fig. 189-3 on p. 1854). FEV_1 declines up to 60 mL/yr in smokers, compared with a less steep decline of 25 to 30 mL/yr in nonsmokers, beginning at about age 30. In middle-aged smokers who already have a low FEV_1, the decline occurs more rapidly. When the FEV_1 falls below about 1 L, patients develop dyspnea with activities of daily living (although dyspnea is more closely related to the degree of air trapping than to the degree of airflow limitation); when the FEV_1 falls below about 0.8 L, patients are at risk of hypoxemia, hypercapnia, and cor pulmonale. FEV_1 and FVC are easily measured with office spirometry and define severity of disease (see Table 192-2) because they correlate with symptoms and mortality. Normal reference values are determined by patient age, sex, and height.

Additional pulmonary function testing is necessary only in specific circumstances,

[**Table 192-1.** Factors that May Help Differentiate Asthma and COPD]

such as before lung volume reduction surgery (see p. 1898). Other test abnormalities may include increased total lung capacity, functional residual capacity, and residual volume, which can help distinguish COPD from restrictive pulmonary disease, in which these measures are diminished; decreased vital capacity; and decreased single-breath diffusing capacity for carbon monoxide (DLCO). Decreased DLCO is nonspecific and is reduced in other disorders that affect the pulmonary vascular bed, such as interstitial lung disease, but can help distinguish emphysema from asthma, in which DLCO is normal or elevated.

Imaging tests: The chest x-ray may have characteristic findings. Changes in emphysema can include lung hyperinflation manifested as a flat diaphragm (ie, increase in the angle formed by the sternum and anterior diaphragm on a lateral film from the normal value of 45° to > 90°), rapid tapering of hilar vessels, and bullae (ie, radiolucencies > 1 cm surrounded by arcuate, hairline shadows). Other typical findings include widening of the retrosternal airspace and a narrow cardiac shadow. Emphysematous changes occurring predominantly in the lung bases suggest α_1-antitrypsin deficiency (see p. 1901). The lungs may look normal or have increased lucency secondary to loss of parenchyma. Among patients with chronic obstructive bronchitis, chest x-rays may be normal or may show a bibasilar increase in bronchovascular markings as a result of bronchial wall thickening.

Prominent hila suggest large central pulmonary arteries that may signify pulmonary hypertension. Right ventricular enlargement that occurs in cor pulmonale may be masked by lung hyperinflation or may manifest as

[**Table 192-2.** Stages and Treatment of COPD]

encroachment of the heart shadow on the retrosternal space or by widening of the transverse cardiac shadow in comparison with previous chest x-rays.

CT may reveal abnormalities that are not apparent on the chest x-ray and may also suggest coexisting or complicating disorders, such as pneumonia, pneumoconiosis, or lung cancer. CT helps assess the extent and distribution of emphysema, estimated either by visual scoring or with analysis of the distribution of lung density. Indications for obtaining CT in patients with COPD include evaluation for lung volume reduction surgery, suspicion of coexisting or complicating disorders that are not clearly evident or excluded by chest x-ray, and suspicion of cancer.

Adjunctive tests: α_1-Antitrypsin levels should be measured in patients < 50 yr with symptomatic COPD and in nonsmokers of any age with COPD to detect α_1-antitrypsin deficiency (see p. 1901). Other indications of α_1-antitrypsin deficiency include a family history of premature COPD or infantile liver disease, lower-lobe distribution of emphysema, and COPD associated with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis. If levels of α_1-antitrypsin are low, the diagnosis should be confirmed by establishing the α_1-antitrypsin phenotype.

ECG, often done to exclude cardiac causes of dyspnea, typically shows diffusely low QRS voltage with a vertical heart axis caused by lung hyperinflation and increased P-wave voltage or rightward shifts of the P-wave vector caused by right atrial enlargement in patients with advanced emphysema. Findings of right ventricular hypertrophy include an R or R´ wave as tall as or taller than the S wave in lead V_1; an R wave smaller than the S wave in lead V_6; right-axis deviation > 110° without right bundle branch block; or some combination of these. Multifocal atrial tachycardia, an arrhythmia that can accompany COPD, manifests as a tachyarrhythmia with polymorphic P waves and variable PR intervals.

Echocardiography is occasionally useful for assessing right ventricular function and pulmonary hypertension, although air trapping makes it technically difficult in patients with COPD. Echocardiography is most often indicated when coexistent left ventricular or valvular heart disease is suspected.

CBC is of little diagnostic value in the evaluation of COPD but may show erythrocythemia (Hct > 48%) if the patient has chronic hypoxemia. Patients with anemia (for reasons other than COPD) have disproportionately severe dyspnea.

Evaluation of exacerbations: Patients with acute exacerbations usually have combinations of increased work of breathing, low O_2 saturation on pulse oximetry, diaphoresis, tachycardia, anxiety, and cyanosis. However, patients with exacerbations accompanied by retention of CO_2 may be lethargic or somnolent, a very different appearance. All patients requiring hospitalization for an acute exacerbation should undergo ABG sampling to quantify hypoxemia and hypercapnia. Hypercapnia may exist with hypoxemia.

Findings of PaO_2 < 50 mm Hg or $PaCO_2$ > 50 mm Hg in the setting of respiratory acidemia define acute respiratory failure (see p. 2279). However, some patients chronically manifest such levels of PaO_2 and $PaCO_2$ in the absence of acute respiratory failure.

A chest x-ray is often done to check for pneumonia or pneumothorax. Very rarely, infiltrates among patients receiving chronic systemic corticosteroids may represent *Aspergillus* pneumonia.

Yellow or green sputum is a reliable indicator of neutrophils in the sputum and suggests bacterial colonization or infection. Culture is usually done in hospitalized patients but is not usually necessary in outpatients. In samples from outpatients, Gram stain usually shows neutrophils with a mixture of organisms, often gram-positive diplococci (*Streptococcus pneumoniae*), gram-negative bacilli (*H. influenzae*), or both. Other oropharyngeal commensal organisms, such as *Moraxella* (*Branhamella*) *catarrhalis*, occasionally cause exacerbations. In hospitalized patients, cultures may show resistant gram-negative organisms (eg, *Pseudomonas*) or, rarely, *Staphylococcus*.

Prognosis

Severity of airway obstruction predicts survival in patients with COPD. The mortality rate in patients with an FEV_1 ≥ 50% of predicted is slightly greater than that of the general population. If the FEV_1 is 0.75 to 1.25 L, 5-yr survival is about 40 to 60%; if < 0.75 L, about 30 to 40%.

More accurate prediction of death risk is possible by simultaneously measuring body mass index (*B*), the degree of airflow obstruction (*O*, which is the FEV_1), dyspnea (*D*, which is measured with a Modified Medical Research Council [MMRC] dyspnea scale), and exercise capacity (*E*, which is measured with a 6-min walking test); this is the BODE index. Also, heart disease, anemia, resting tachycardia, hypercapnia, and hypoxemia decrease survival, whereas a significant response to bronchodilators predicts improved survival. Risk factors for death in patients with acute exacerbation requiring hospitalization include older age, higher $PaCO_2$, and use of maintenance oral corticosteroids.

Patients at high risk of imminent death are those with progressive unexplained weight loss or severe functional decline (eg, those who experience dyspnea with self-care, such as dressing, bathing, or eating). Mortality in COPD may result from intercurrent illnesses rather than from progression of the underlying disorder in patients who have stopped smoking. Death is generally caused by acute respiratory failure, pneumonia, lung cancer, heart disease, or pulmonary embolism.

Treatment of Stable COPD

• Inhaled bronchodilators, corticosteroids, or both

• Supportive care (eg, smoking cessation, O_2 therapy, pulmonary rehabilitation)

COPD management involves treatment of chronic stable disease and of exacerbations. Treatment of cor pulmonale, a common complication of long-standing, severe COPD, is discussed elsewhere (see p. 2133).

Treatment of chronic stable COPD aims to prevent exacerbations and improve lung and physical function through drug and O_2 therapy, smoking cessation, exercise, enhancement of nutrition, and pulmonary rehabilitation. Surgical treatment of COPD is indicated for selected patients.

Drug therapy: Recommended drug therapy is summarized in Table 192-2.

Inhaled bronchodilators are the mainstay of COPD management; drugs include

• β-agonists

• Anticholinergics (antimuscarinics)

These two classes are equally effective. Patients with mild (stage 1) disease are treated only when symptomatic. Those with stage 2 or higher COPD should be taking drugs from one or both of these classes regularly to improve pulmonary function and increase exercise capacity. The frequency of exacerbations can be reduced with the use of anticholinergics, inhaled corticosteroids, or long-acting β-agonists. However, there is no evidence that regular bronchodilator use slows deterioration of lung function. The initial choice among short-acting β-agonists, long-acting β-agonists, anticholinergics (which have a greater bronchodilating effect), and combination β-agonist and anticholinergic therapy is often a matter of tailoring cost and convenience to the patient's preferences and symptoms.

In treatment of chronic stable disease, administration by metered-dose inhaler or dry-powder inhaler is preferred over nebulized home treatment; home nebulizers are prone to contamination from incomplete cleaning and drying. Patients should be taught to exhale to functional residual capacity, inhale the aerosol slowly to total lung capacity, and hold the inhalation for 3 to 4 sec before exhaling. Spacers help ensure optimal delivery of drug to the distal airways and reduce the importance of coordinating activation of the inhaler with inhalation. Some spacers alert patients if they are inhaling too rapidly. Newer metered-dose inhalers that use hydrofluoroalkane (HFA) propellants require slightly different techniques than inhalers containing older environmentally damaging chlorinated fluorocarbon propellants; inhalers containing HFA require 2 to 3 priming doses if they are new or not recently used.

β-Agonists relax bronchial smooth muscle and increase mucociliary clearance. Albuterol aerosol, 2 puffs (90 to 100 µg/puff) inhaled from a metered-dose inhaler 4 to 6 times/day prn, is usually the drug of choice because of low cost. Long-acting β-agonists are preferable for patients with nocturnal symptoms or for those who find frequent dosing inconvenient. Options include salmeterol powder, 1 puff (50 µg) inhaled bid, and formoterol powder, 1 puff (12 µg) inhaled bid. The dry-powder formulations may be more effective for patients who have trouble coordinating use of a metered-dose inhaler. Patients should be taught the difference between short-acting and long-acting drugs, because long-acting drugs that are used as needed or more than twice/day increase the risk of cardiac arrhythmias. Adverse effects commonly result from use of any β-agonist and include tremor, anxiety, tachycardia, and mild, temporary hypokalemia.

Anticholinergics relax bronchial smooth muscle through competitive inhibition of muscarinic receptors (M_1, M_2, and M_3). Ipratropium is most commonly used because of low cost and ready availability; dose is 2 to 4 puffs (18 µg/puff) from a metered-dose inhaler q 4 to 6 h. Ipratropium has a slower onset of action (within 30 min; peak effect in 1 to 2 h), so a β_2-agonist is often prescribed with it in a single combination inhaler or as a separate as-needed rescue drug. Tiotropium, a long-acting quaternary anticholinergic inhaled as a powder formulation, is M_1 and M_3 selective and may therefore have an advantage over ipratropium, because M_2 receptor blockade (as occurs with ipratropium) may limit bronchodilation. Dose is 1 puff (18 µg) once/day. Adverse effects of all anticholinergics are pupillary dilation, blurred vision, and dry mouth.

Corticosteroids are often part of treatment. Inhaled corticosteroids seem to reduce airway inflammation, reverse β-receptor down-regulation, and inhibit leukotriene and cytokine production. They do not alter the course of pulmonary function decline in patients with COPD who continue to smoke, but they do relieve symptoms and improve short-term pulmonary function in some patients, are additive to the effect of bronchodilators, and may diminish the frequency of COPD exacerbations. They are indicated for patients who have repeated exacerbations or symptoms despite optimal bronchodilator therapy. Dose depends on the drug; examples include fluticasone 500 to 1000 µg/day and beclomethasone 400 to 2000 µg/day. The long-term risks of inhaled corticosteroids in elderly people are not proved but probably include osteoporosis, cataract formation, and an increased risk of nonfatal pneumonia. Long-term users therefore should undergo periodic ophthalmologic and bone densitometry screening and should possibly receive supplemental calcium, vitamin D, and a bisphosphonate as indicated. Corticosteroid therapy should be stopped if no subjective or objective improvement results (eg, after a few months).

Combinations of a long-acting β-agonist (eg, salmeterol) and an inhaled corticosteroid (eg, fluticasone) are more effective than either drug alone in the treatment of chronic stable disease.

Oral or systemic corticosteroids should usually not be used to treat chronic stable COPD.

Theophylline plays only a small role in the treatment of chronic stable COPD now that safer, more effective drugs are available. Theophylline decreases smooth muscle spasm, enhances mucociliary clearance, improves right ventricular function, and decreases pulmonary vascular resistance and arterial pressure. Its mode of action is poorly understood but appears to differ from that of β_2-agonists and anticholinergics. Its role in improving diaphragmatic function and dyspnea during exercise is controversial. Low-dose theophylline (300 to 400 mg/day) has anti-inflammatory properties and may enhance the effects of inhaled corticosteroids.

Theophylline can be used for patients who have not adequately responded to inhaled drugs and who have shown symptomatic benefit from a trial of the drug. Serum levels need not be monitored unless the patient does not respond to the drug, develops symptoms of toxicity, or is questionably adherent; slowly absorbed oral theophylline preparations, which require less frequent dosing, enhance adherence. Toxicity is common and includes sleeplessness and GI upset, even at low blood levels. More serious adverse effects, such as supraventricular and ventricular arrhythmias and seizures, tend to occur at blood levels > 20 mg/L. Hepatic metabolism of theophylline varies greatly and is influenced by genetic factors, age, cigarette smoking, hepatic dysfunction, and some drugs, such as macrolide and fluoroquinolone antibiotics and nonsedating histamine$_2$ blockers.

Oxygen therapy: Long-term O_2 therapy prolongs life in patients with COPD whose PaO_2 is chronically < 55 mm Hg. Continual 24-h use is more effective than a 12-h nocturnal regimen. O_2 therapy brings Hct toward normal levels; improves neuropsychologic factors, possibly by facilitating sleep; and ameliorates pulmonary hemodynamic abnormalities. O_2 therapy also increases exercise tolerance in many patients.

O_2 saturation should be measured during exercise and while at rest. Similarly, a sleep study should be considered for patients with advanced COPD who do not meet the criteria for long-term O_2 therapy while they are awake (see
Table 192-3) but whose clinical assessment suggests pulmonary hypertension in the absence of daytime hypoxemia. Nocturnal O_2 may be prescribed if a sleep study shows episodic desaturation to ≤ 88%. Such treatment prevents progression of pulmonary hypertension, but its effects on survival are unknown.

O_2 is administered by nasal cannula at a flow rate sufficient to achieve a PaO_2 > 60 mm Hg (SaO_2 > 90%), usually ≤ 3 L/min at rest. O_2 is supplied by electrically driven O_2 concentrators, liquid O_2 systems, or cylinders of compressed gas. Concentrators, which limit mobility but are the least expensive, are preferable for patients who spend most of their time at home. Such patients require small O_2 tanks for backup in case of an electrical failure and for portable use.

[**Table 192-3.** Indications for Long-Term O_2 Therapy in COPD]

A liquid system is preferable for patients who spend much time out of their home. Portable canisters of liquid O_2 are easier to carry and have more capacity than portable cylinders of compressed gas. Large compressed-air cylinders are the most expensive way of providing O_2 and should be used only if no other source is available. All patients must be taught the dangers of smoking during O_2 use.

Various O_2-conserving devices can reduce the amount of O_2 used by the patient, either by using a reservoir system or by permitting O_2 flow only during inspiration. Systems with these devices correct hypoxemia as effectively as do continuous flow systems.

Some patients need supplemental O_2 during air travel, because flight cabin pressure in commercial airliners is below sea level air pressure (often equivalent to 1830 to 2400 m [6000 to 8000 ft]). Eucapnic COPD patients who have a PaO_2 > 68 mm Hg at sea level generally have an in-flight PaO_2 > 50 mm Hg and do not require supplemental O_2. All patients with COPD with a PaO_2 ≤ 68 mm Hg at sea level, hypercapnia, significant anemia (Hct < 30), or a coexisting heart or cerebrovascular disorder should use

supplemental O_2 during long flights and should notify the airline when making their reservation. Airlines can provide supplemental O_2, and most require a minimum notice of 24 h, a physician's statement of necessity, and an O_2 prescription before the flight. Patients should bring their own nasal cannulas, because some airlines provide only face masks. Patients are not permitted to transport or use their own liquid O_2, but many airlines now permit use of portable battery-operated O_2 concentrators, which also provide a suitable O_2 source on arrival.

Smoking cessation: Smoking cessation (see p. 3432) is both extremely difficult and extremely important; it slows but does not halt the rate of FEV_1 decline (see Fig. 192-1). Simultaneous use of multiple strategies is most effective: establishment of a quit date, behavior modification techniques, group sessions, nicotine replacement therapy (by gum, transdermal patch, inhaler, lozenge, or nasal spray), varenicline or bupropion, and physician encouragement. Quit rates > 50% at 1 yr have not been demonstrated even with the most effective interventions, such as use of bupropion combined with nicotine replacement or use of varenicline alone.

Vaccinations: All patients with COPD should be given annual influenza vaccinations. If a patient is unable to receive a vaccination or if the prevailing influenza strain is not included in the annual vaccine formulation, prophylactic treatment (amantadine, rimantadine, oseltamivir, or zanamivir) is appropriate during community influenza outbreaks. Pneumococcal polysaccharide vaccine, although of unproven efficacy in COPD, has minimal adverse effects and should probably also be given.

Nutrition: COPD patients are at risk of weight loss and nutritional deficiencies because of a 15 to 25% increase in resting energy expenditure from breathing; a higher energy cost of daily activities; reduced caloric intake relative to need because of dyspnea; and the catabolic effect of inflammatory cytokines such as TNF-α. Generalized muscle strength and efficiency of O_2 use are impaired. Patients with poorer nutritional status have a worse prognosis, so it is prudent to recommend a balanced diet with adequate caloric intake in conjunction with exercise to prevent or reverse undernutrition and muscle atrophy. However, excessive weight gain should be avoided, and obese patients should strive to gradually reduce body fat. Studies of nutritional supplementation alone have not shown improvement in pulmonary function or exercise capacity. Trials of anabolic steroids (eg, megestrol, oxandrolone), growth

[**Fig. 192-1.** Patients who quit smoking compared with those who continue.]

hormone supplementation, and TNF antagonists in reversing undernutrition and improving functional status and prognosis in COPD have been disappointing.

Pulmonary rehabilitation: Pulmonary rehabilitation programs serve as adjuncts to drug treatment to improve physical function; many hospitals and health care organizations offer formal multidisciplinary rehabilitation programs. Pulmonary rehabilitation includes exercise, education, and behavioral interventions. Treatment should be individualized; patients and family members are taught about COPD and medical treatments, and patients are encouraged to take as much responsibility for personal care as possible. The benefits of rehabilitation are greater independence and improved quality of life and exercise capacity. Pulmonary rehabilitation typically does not improve pulmonary function or increase longevity, however. A carefully integrated rehabilitation program helps patients with severe COPD accommodate to physiologic limitations while providing realistic expectations for improvement. Patients with severe disease require a minimum of 3 mo of rehabilitation to benefit and should continue with maintenance programs.

An exercise program can be helpful in the home, in the hospital, or in institutional settings. Graded exercise can ameliorate skeletal muscle deconditioning resulting from inactivity or prolonged hospitalization for respiratory failure. Specific training of respiratory muscles is less helpful than general aerobic conditioning.

A typical training program begins with slow walking on a treadmill or unloaded cycling on an ergometer for a few minutes. Duration and exercise load are progressively increased over 4 to 6 wk until the patient can exercise for 20 to 30 min nonstop with manageable dyspnea. Patients with very severe COPD can usually achieve an exercise regimen of walking for 30 min at 1 to 2 mph. Maintenance exercise should be done 3

to 4 times/wk to maintain fitness levels. O_2 saturation is monitored, and supplemental O_2 is provided as needed.

Upper extremity resistance training helps the patient in doing daily tasks (eg, bathing, dressing, house cleaning). The usual benefits of exercise are modest increases in lower extremity strength, endurance, and maximum O_2 consumption.

Patients should be taught ways to conserve energy during activities of daily living and to pace their activities. Difficulties in sexual function should be discussed and advice should be given on using energy-conserving techniques for sexual gratification.

Surgery: Surgical options for treatment of severe COPD include lung volume reduction and transplantation.

Lung volume reduction surgery consists of resecting nonfunctioning emphysematous areas. The procedure improves exercise tolerance and decreases 2-yr mortality in patients with severe, predominantly upper-lung emphysema who have low baseline exercise capacity after pulmonary rehabilitation. Other patients may experience symptom relief and improved exercise capacity after surgery, but mortality has been the same as or increased when compared with that for drug therapy. The effect on ABGs is variable and not predictable, but most patients who require O_2 before surgery continue to need it. Long-term effects of the procedure are unknown. Improvement is less than that with lung transplantation. The mechanism of improvement is believed to be enhanced lung recoil and improved diaphragmatic function. Operative mortality is about 5%. The best candidates for lung volume reduction surgery are patients with an FEV_1 20 to 40% of predicted, a DLCO > 20% of predicted, significantly impaired exercise capacity, heterogeneous pulmonary disease on CT with an upper-lobe predominance, $PaCO_2$ < 50 mm Hg, and absence of severe pulmonary hypertension and coronary artery disease.

Rarely, patients have extremely large bullae that compress the functional lung. These patients can be helped by surgical resection of these bullae, with resulting relief of symptoms and improved pulmonary function. Generally, resection is most beneficial for patients with bullae affecting more than one third of a hemithorax and an FEV_1 about half of the predicted normal value. Improved pulmonary function is related to the amount of normal or minimally diseased lung tissue that was compressed by the resected bullae. Serial chest x-rays and CT scans are the most useful procedures for determining whether a patient's functional status is due to compression of viable lung by bullae or to generalized emphysema. A markedly reduced DLCO (< 40% predicted) indicates widespread emphysema and suggests a poorer outcome from surgical resection.

Single-lung transplantation has largely replaced double-lung transplantation in patients with COPD. Candidates for transplantation are patients < 60 to 65 yr with an FEV_1 < 25% predicted after bronchodilator therapy or with severe pulmonary hypertension. The goal of lung transplantation is to improve quality of life, because survival time is rarely increased. The 5-yr survival after transplantation for emphysema is 45 to 60%. Lifelong immunosuppression is required, with the attendant risk of opportunistic infections.

Treatment of Acute COPD Exacerbation

- O_2 supplementation
- Bronchodilators
- Corticosteroids
- Antibiotics
- Sometimes ventilatory assistance

The immediate objectives are to ensure adequate oxygenation and near-normal blood pH, reverse airway

obstruction, and treat any cause.

The cause of an acute exacerbation is usually unknown, although some acute exacerbations result from bacterial or viral infections. Smoking, irritative inhalational exposure, and high levels of air pollution also contribute. Mild exacerbations often can be treated on an outpatient basis in patients with adequate home support. Elderly, frail patients and patients with comorbidities, a history of respiratory failure, or acute changes in ABG measurements are admitted to the hospital for observation and treatment. Patients with life-threatening exacerbations manifested by uncorrected moderate to severe acute hypoxemia, acute respiratory acidosis, new arrhythmias, or deteriorating respiratory function despite hospital treatment should be admitted to the ICU and their respiratory status monitored frequently.

Oxygen: Most patients require O_2 supplementation, even those who do not need it chronically. Hypercapnia may worsen in patients given O_2. This worsening has traditionally been thought to result from an attenuation of hypoxic respiratory drive. However, increased V/Q mismatch probably is a more important factor. Before O_2 administration, pulmonary vasoconstriction minimizes V/Q mismatch by decreasing perfusion of the most poorly ventilated areas of the lungs. Increased V/Q mismatch occurs because O_2 administration attenuates this hypoxic pulmonary vasoconstriction. The Haldane effect may also contribute to worsening hypercapnia, although this theory is controversial. The Haldane effect is a decrease in Hb's affinity for CO_2, which results in increased amounts of CO_2 dissolved in plasma. O_2 administration, even though it may worsen hypercapnia, is recommended; many patients with COPD have chronic as well as acute hypercapnia and thus severe CNS depression is unlikely unless $PaCO_2$ is > 85 mm Hg. The target level for PaO_2 is about 60 mm Hg; higher levels offer little advantage and increase the risk of hypercapnia. O_2 is given via Venturi mask so it can be closely regulated, and the patient is closely monitored. Patients whose condition deteriorates with O_2 therapy (eg, those with severe acidemia or CNS depression) require ventilatory assistance.

Many patients who require home O_2 for the first time when they are discharged from the hospital after an exacerbation improve within 30 days and no longer require O_2. Thus, the need for home O_2 should be reassessed 60 to 90 days after discharge.

Ventilatory assistance: Noninvasive positivepressure ventilation (eg, pressure support or bilevel positive airway pressure ventilation by face mask—see p. 2282) is an alternative to full mechanical ventilation. Noninvasive ventilation appears to decrease the need for intubation, reduce hospital stay, and reduce mortality in patients with severe exacerbations (defined as a pH < 7.30 in hemodynamically stable patients not at immediate risk of respiratory arrest). Noninvasive ventilation appears to have no effect in patients with less severe exacerbation. However, it may be indicated for patients with less severe exacerbations whose ABGs worsen despite initial drug or O_2 therapy or who appear to be imminent candidates for full mechanical ventilation but who do not require intubation for control of the airway or sedation for agitation. Deterioration while receiving noninvasive ventilation necessitates invasive mechanical ventilation.

Deteriorating ABG values and mental status and progressive respiratory fatigue are indications for endotracheal intubation and mechanical ventilation. Ventilator settings, management strategies, and complications are discussed elsewhere (see p. 2281). Risk factors for ventilatory dependence include an FEV_1 < 0.5 L, stable ABGs with a PaO_2 < 50 mm Hg, or a $PaCO_2$ > 60 mm Hg, severe exercise limitation, and poor nutritional status. Therefore, a discussion of patients' wishes regarding intubation and mechanical ventilation should be initiated and documented (see p. 3471). However, overconcern about possible ventilator dependence should not delay management of acute respiratory failure; many patients who require mechanical ventilation can return to their pre-exacerbation level of health.

In patients who require prolonged intubation (eg, > 2 wk), a tracheostomy is indicated to facilitate comfort, communication, and eating. With a good multidisciplinary rehabilitation program, including nutritional and psychologic support (see p. 1867), many patients who require prolonged mechanical ventilation can be successfully liberated and can return to their former level of function. Specialized programs are available

for patients who remain ventilator-dependent after acute respiratory failure. Some patients can remain off the ventilator during the day. For patients with adequate home support, training of family members can permit some patients to be sent home with ventilators.

Drug therapy: β-Agonists and anticholinergics, with or without corticosteroids, should be started concurrently with O_2 therapy (regardless of how O_2 is administered) with the aim of reversing airway obstruction. Methylxanthines, once considered essential to treatment of acute COPD exacerbations, are no longer used; toxicities exceed benefits.

Short-acting β-agonists are the cornerstone of drug therapy for acute exacerbations. The most widely used drug is albuterol 2.5 mg by nebulizer or 2 to 4 puffs (100 µg/puff) by metered-dose inhaler q 2 to 6 h. Inhalation using a metered-dose inhaler causes rapid bronchodilation; there are no data indicating that doses taken with nebulizers are more effective than the same doses correctly taken with metered-dose inhalers. In life-threatening exacerbations, risks of the exacerbation usually exceed those of high-dose α-agonists; thus, β-agonists may be given continuously via nebulizer until improvement occurs.

Ipratropium, the most commonly used anticholinergic, is effective in acute COPD exacerbations and should be given concurrently or alternating with β-agonists. Dosage is 0.25 to 0.5 mg by nebulizer or 2 to 4 inhalations (17 to 18 µg of drug delivered per puff) by metered-dose inhaler q 4 to 6 h. Ipratropium generally provides bronchodilating effect similar to that of usual recommended doses of α-agonists. The role of the longer-acting anticholinergic tiotropium in treating acute exacerbations has not been defined.

Corticosteroids should be begun immediately for all but mild exacerbations. Options include prednisone 30 to 60 mg po once/day for 5 days or tapered over 7 to 14 days, or methylprednisolone 60 to 500 mg IV once/day for 3 days and then tapered over 7 to 14 days. These drugs are equivalent in their acute effects; inhaled corticosteroids have no role in the treatment of acute exacerbations.

Antibiotics are recommended for exacerbations in patients with purulent sputum. Some physicians give antibiotics empirically for change in sputum color or for nonspecific chest x-ray abnormalities. Routine cultures and Gram stains are not necessary before treatment unless an unusual or resistant organism is suspected (eg, in hospitalized, institutionalized, or immunosuppressed patients). Drugs directed against oral flora are indicated. Trimethoprim/sulfamethoxazole 160 mg/800 mg po bid, amoxicillin 250 to 500 mg po tid, tetracycline 250 mg po qid, and doxycycline 50 to 100 mg po bid given for 7 to 14 days are all effective and inexpensive. Choice of drug is dictated by local patterns of bacterial sensitivity and patient history. If the patient is seriously ill or if clinical evidence suggests that the infectious organisms are resistant, more expensive 2nd-line drugs can be used. These drugs include amoxicillin/clavulanate 250 to 500 mg po tid, fluoroquinolones (eg, ciprofloxacin, levofloxacin), 2nd-generation cephalosporins (eg, cefuroxime, cefaclor), and extended-spectrum macrolides (eg, azithromycin, clarithromycin). These drugs are effective against β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* but have not been shown to be more effective than first-line drugs for most patients. Patients can be taught to recognize a change in sputum from normal to purulent as a sign of impending exacerbation and to start a 10- to 14-day course of antibiotic therapy. Long-term antibiotic prophylaxis is recommended only for patients with underlying structural changes in the lung, such as bronchiectasis or infected bullae.

Antitussives, such as dextromethorphan and benzonatate, have little role.

Opioids (eg, codeine, hydrocodone, oxycodone) should be used judiciously for relief of symptoms (eg, severe coughing paroxysms, pain) insofar as these drugs may suppress a productive cough, impair mental status, and cause constipation.

End-of-life care: With very severe disease, particularly when death is imminent, exercise is unwarranted and activities of daily living are arranged to minimize energy expenditure. For example, patients may arrange to live on one floor of the house, have several small meals rather than fewer large meals, and avoid wearing shoes that must be tied. End-of-life care should be discussed, including whether to pursue mechanical ventilation, the use of palliative sedation, and appointment of a surrogate medical decision-maker in the event of the patient's incapacitation.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is congenital lack of a primary lung antiprotease, α_1-antitrypsin, which leads to increased protease-mediated tissue destruction and emphysema in adults. Hepatic accumulation of abnormal α_1-antitrypsin can cause liver disease in both children and adults. Serum α_1-antitrypsin level < 11 µmol/L (< 80 mg/dL) confirms the diagnosis. Treatment is smoking cessation, bronchodilators, early treatment of infection, and, in selected cases, α_1-antitrypsin replacement. Severe liver disease may require transplantation. Prognosis is related mainly to degree of lung impairment.

Pathophysiology

α_1-Antitrypsin is a neutrophil elastase inhibitor (an antiprotease), the major function of which is to protect the lungs from proteasemediated tissue destruction. Most α_1-antitrypsin is synthesized by hepatocytes and monocytes and passively diffuses through the circulation into the lungs; some is secondarily produced by alveolar macrophages and epithelial cells. The protein conformation (and hence functionality) and quantity of circulating α_1-antitrypsin are determined by codominant expression of parental alleles; > 90 different alleles have been identified and described by protease inhibitor (PI*) phenotype.

Liver: Inheritance of some variant alleles causes a change in conformation of the α_1-antitrypsin molecule, leading to polymerization and retention within hepatocytes. The hepatic accumulation of aberrant α_1-antitrypsin molecules causes neonatal cholestatic jaundice in 10 to 20% of patients; the remaining patients are probably able to degrade the abnormal protein, although the exact protective mechanism is unclear. About 20% of cases of neonatal hepatic involvement result in development of cirrhosis in childhood. About 10% of patients without childhood liver disease develop cirrhosis as adults. Liver involvement increases the risk of liver cancer.

Lungs: In the lungs, α_1-antitrypsin deficiency increases neutrophil elastase activity, which facilitates tissue destruction leading to emphysema (especially in smokers, because cigarette smoke also increases protease activity). α_1-Antitrypsin deficiency accounts for 1 to 2% of all cases of COPD. α_1-Antitrypsin deficiency most commonly causes early emphysema; symptoms and signs of lung involvement occur earlier in smokers than in nonsmokers but in both cases are rare before age 25.

Other tissues: Other disorders possibly associated with α_1-antitrypsin allele variants include panniculitis (an inflammatory disorder of the subcutaneous tissue), life-threatening hemorrhage (through a mutation that converts α_1-antitrypsin from a neutrophil elastase to a coagulation factor inhibitor), aneurysms, ulcerative colitis, antineutrophilic cytoplasmic antibody (ANCA)-positive vasculitis, and glomerular disease.

Classification

The normal PI phenotype is PI*MM. More than 95% of people with severe α_1-antitrypsin deficiency and emphysema are homozygous for the Z allele (PI*ZZ) and have α_1-antitrypsin levels of about 30 to 40 mg/dL (5 to 6 µmol/L). Prevalence in the general population is 1/1500 to 1/5000. Most are whites of Northern European descent; the Z allele is rare in people of Asian descent and blacks. Though emphysema is common among PI*ZZ patients, many nonsmoking patients who are homozygous for PI*ZZ do not develop emphysema; patients who do typically have a family history of COPD. PI*ZZ smokers have a lower life expectancy than PI*ZZ nonsmokers, who have a lower life expectancy than PI*MM nonsmokers and smokers. Nonsmoking people who are PI*MZ heterozygous are more likely to experience more rapid decreases in forced expiratory volume in 1 sec (FEV_1) over time than do people in the general population.

Other rare phenotypes include PI*SZ and two types with nonexpressing alleles, PI*Z-null and PI*null-null (see Table 192-4). The null phenotype leads to undetectable serum levels of α_1-antitrypsin. Normal serum

levels of malfunctioning α_1-antitrypsin may occur with rare mutations.

Symptoms and Signs

Neonates with hepatic involvement present with cholestatic jaundice and hepatomegaly during the first week of life; jaundice usually resolves by 2 to 4 mo of age. Cirrhosis may develop in childhood or adulthood (symptoms and signs of cirrhosis and hepatocellular carcinoma are discussed elsewhere in THE MANUAL). Adults with emphysema have symptoms and signs of COPD (see p. 1891), including dyspnea, cough, wheezing, and prolonged expiration. Severity of pulmonary disease varies greatly depending on phenotype, smoking status, and other factors. Pulmonary function is well preserved in some PI*ZZ smokers and can be severely impaired in some PI*ZZ nonsmokers. PI*ZZ people identified in

[**Table 192-4.** Expression of Phenotype in α_1-Antitrypsin Deficiency]

population surveys (ie, those without symptoms or pulmonary disease) tend to have better pulmonary function, whether they smoke or not, than do index people (those identified because they have pulmonary disease). Airflow obstruction occurs more frequently in men and in people with asthma, recurrent respiratory infections, occupational dust exposure, and a family history of pulmonary disease.

Panniculitis, an inflammatory disorder of subcutaneous soft tissue, manifests as indurated, tender, discolored plaques or nodules, typically on the lower abdomen, buttocks, and thighs (see p. 687).

Diagnosis

• Serum α_1-antitrypsin level

• Genotyping

α_1-Antitrypsin deficiency is suspected in the following:

• Smokers who develop emphysema before age 45

• Nonsmokers without occupational exposures who develop emphysema at any age

• Patients whose chest x-ray shows predominately lower lung emphysema

• Patients with a family history of emphysema or unexplained cirrhosis

• Patients with panniculitis

• Neonates with jaundice or liver enzyme elevations

• Patients with unexplained bronchiectasis or liver disease

Diagnosis is made by identifying serum α_1-antitrypsin levels < 80 mg/dL (< 11 µmol/L) if measured by the radial immunodiffusion method or levels < 50 mg/dL (< 6.9 µmol/L) if measured by nephelometry. Patients with low levels should have confirmation by genotyping.

Prognosis

As a group, people with severe α_1-antitrypsin deficiency who have never smoked have a normal life expectancy and only moderate impairment of pulmonary function. The most common cause of death in α_1-antitrypsin deficiency is emphysema, followed by cirrhosis, often with hepatic carcinoma.

Treatment

• Supportive care

• For pulmonary disease, often α_1-antitrypsin replacement

Treatment of pulmonary disease is with purified human α_1-antitrypsin (60 mg/kg IV over 45 to 60 min given once/wk or 250 mg/kg over 4 to 6 h given once/mo [pooled only]), which can maintain the serum α_1-antitrypsin level above a target protective level of 80 mg/dL (35% of normal). Because emphysema causes permanent structural change, therapy cannot repair damaged lung structure or improve lung function but is given to halt progression. Treatment is expensive and is therefore reserved for nonsmoking patients in whom both alleles are abnormal and who have mild to moderately abnormal pulmonary function and confirmation of diagnosis by low serum α_1-antitrypsin levels. It is not indicated for patients who have severe disease or for patients in whom one or both alleles are normal.

Smoking cessation, use of bronchodilators, and early treatment of respiratory infections are particularly important for α_1-antitrypsin-deficient patients with emphysema. Experimental treatments, such as phenyl butyric acid that can reverse the misfolding of the abnormal α_1-antitrypsin proteins in the hepatocytes, thereby stimulating protein release, are being investigated. For severely impaired people < 60 yr, lung transplantation should be considered. Lung volume reduction in treating the emphysema of α_1-antitrypsin deficiency is controversial. Gene therapy is under study.

Treatment of liver disease is supportive. Enzyme replacement does not help because the disease is caused by abnormal processing rather than by enzyme deficiency. Liver transplantation may be used for patients with liver failure.

Treatment of panniculitis is not well defined. Corticosteroids, antimalarials, and tetracyclines have been used.

Chapter 193. Sleep Apnea

Introduction

Breathing disorders that occur during sleep include obstructive sleep apnea and central sleep apnea. Less severe forms include snoring and upper airway resistance syndrome. The term sleep-disordered breathing is used to encompass all such disorders. (See also Ch. 177.)

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) consists of episodes of partial or complete closure of the upper airway that occur during sleep and lead to breathing cessation (defined as a period of apnea > 10 sec). Symptoms include restlessness, snoring, recurrent awakening, morning headache, and excessive daytime sleepiness. Diagnosis is based on sleep history and polysomnography. Treatment is with nasal continuous positive airway pressure, oral appliances, and, in refractory cases, surgery. Prognosis is good with treatment. Most cases remain undiagnosed and untreated and are often associated with hypertension, heart failure, and injury or death due to motor vehicle crashes and other accidents resulting from hypersomnolence.

In at-risk patients, sleep destabilizes patency of the upper airway, leading to partial or complete obstruction of the nasopharynx, oropharynx, or both. When breathing is diminished but not absent, the condition is called obstructive sleep hypopnea.

The prevalence of OSA is 2 to 9% in adults; the condition is under-recognized and often undiagnosed even in symptomatic patients. OSA is up to 4 times more common among men and 7 times more common among people who are obese (ie, body mass index [BMI] > 30). Severe OSA (apnea-hypopnea index [AHI] > 30/h) increases the risk of death in middle-aged men.

Etiology

Anatomic risk factors include obesity, an oropharynx "crowded" by a short or retracted mandible, a prominent tongue base or tonsils, a rounded head shape and a short neck, a neck circumference > 43 cm, thick lateral pharyngeal walls, or lateral parapharyngeal fat pads. Other identified risk factors include postmenopausal status, aging, and alcohol or sedative use. A family history of sleep apnea is present in 25 to 40% of cases, perhaps reflective of intrinsic ventilatory drive or craniofacial structure. The likelihood of other family members having sleep apnea increases as more family members have it.

Many people with OSA have disorders such as hypertension, stroke, diabetes, gastroesophageal reflux disease, nocturnal angina, heart failure, acromegaly, and hypothyroidism. OSA can also be associated with cardiac arrhythmias (eg, atrial fibrillation).

Because obesity is a common risk factor for both OSA and obesity-hypoventilation syndrome (see p. 57), the two conditions may coexist.

Airway obstruction causes paroxysms of inspiratory effort, reductions in gas exchange, disruption of normal sleep architecture, and partial or complete arousals from sleep. Factors that may interact to cause the characteristic symptoms and signs include hypoxia, hypercapnia, and sleep fragmentation.

OSA is an extreme form of sleep-related upper airway resistance. Less severe forms that do not cause O_2 desaturation include snoring; pharyngeal airflow resistance causing noisy inspiration but without sleep arousals; and upper airway resistance syndrome, characterized by crescendo snoring terminated by respiratory effort-related arousals (RERAs). People with upper airway resistance syndrome are typically younger and less obese than those with OSA and they complain of daytime sleepiness more than do those with primary snoring. The symptoms, diagnostic evaluation, and treatment of snoring and upper airway resistance syndrome are otherwise the same as for OSA.

Symptoms and Signs

Although loud disruptive snoring is reported by 85% of OSA patients, most people who snore do not have OSA. Other symptoms of OSA may include choking, gasping, or snorting during sleep, restless and unrefreshing sleep, and difficulty staying asleep. Most patients are unaware of these symptoms (because they occur during sleep) but are informed of them by bed partners, roommates, or housemates.

When awake, patients may experience hypersomnolence, fatigue, and impaired concentration. The frequency of sleep complaints and the degree of daytime sleepiness do not correlate well with number of nocturnal arousals.

Diagnosis

• Symptom criteria

• Sleep studies

The diagnosis is suspected in patients with identifiable risk factors, symptoms, or both. Criteria for diagnosis consist of daytime symptoms, nighttime symptoms, and sleep monitoring that documents > 5 episodes of hypopnea and apnea per hour. Specifically, in regard to symptoms, there should be ≥ 1 of the following:

• Daytime sleepiness, unintentional sleep episodes, unrefreshing sleep, fatigue, or insomnia

• Awakening with breath holding, gasping, or choking

• Reports by a bed partner of loud snoring, breathing interruptions, or both in the patient's sleep

The patient and any bed partners, roommates, or housemates should be interviewed. The differential diagnosis of excessive daytime sleepiness is broad (see p. 1710) and includes

• Reduced quantity or quality of sleep due to poor sleep hygiene

• Sedation or mental status changes due to drugs, chronic diseases (including cardiovascular or respiratory diseases), metabolic disturbances, and accompanying therapies

• Depression

• Alcohol or drug abuse

• Narcolepsy

• Other primary sleep disorders (eg, periodic limb movement disorder, restless legs syndrome)

An extended sleep history should be taken in all patients who

• Are over the age of about 65

• Report daytime fatigue, sleepiness, or insomnia

• Are overweight (BMI > 30)

• Have poorly controlled hypertension (which may be caused or exacerbated by OSA), heart failure (which may cause OSA), stroke, or diabetes

Most patients who report only snoring, without other symptoms or cardiovascular risks, do not need an extensive evaluation for OSA.

The physical examination should include evaluation for nasal obstruction, tonsillar hypertrophy, and

pharyngeal structure and identification of clinical features of hypothyroidism and acromegaly.

The diagnosis is confirmed with polysomnography (see p. 1706), which includes continuous measurement of breathing effort by plethysmography, airflow at the nose and mouth using flow sensors, O_2 saturation by oximetry, sleep architecture by EEG, chin electromyography (looking for hypotonia), and electro-oculograms to assess the occurrence of rapid eye movements. Polysomnography records and helps classify stages of sleep and the occurrence and duration of apneic and hypopneic periods. The patient is also observed by video, and ECG monitoring is used to determine whether arrhythmias occur in conjunction with the apneic episodes. Other variables evaluated include limb muscle activity (to assess nonrespiratory causes of sleep arousal, such as restless legs syndrome and periodic limb movements disorder) and body position (apnea may occur only in the supine position).

The common summary measure used to describe respiratory disturbances during sleep is the AHI, which is the total number of episodes of apnea and hypopnea occurring during sleep divided by the hours of sleep time. AHI values can be computed for different sleep stages. The respiratory disturbance index (RDI) is a similar measure, describing the number of times per hour that blood O_2 saturation falls > 3% but also includes RERAs. If EEG monitoring is used, an arousal index (AI) can be computed, which is the number of arousals per hour of sleep. The AI may be correlated with AHI or RDI, but about 20% of apneas and desaturation episodes are not accompanied by arousals, or other causes of arousals are present. An AHI > 5 is required for the diagnosis of OSA; a value of > 15 indicates a moderate level of sleep apnea and a value > 30 indicates a severe level of apnea. Snoring loudly enough to be heard in the next room confers a 10-fold increase in the likelihood of having AHI > 5. The AI and RDI correlate only moderately with a patient's symptoms.

Ambulatory diagnostic tools are being used more often to diagnose OSA. Portable monitors can measure heart rate, pulse oximetry, effort, position, and nasal airflow to provide estimates of respiratory disturbances during self-reported sleep, thereby providing a value for AHI/RDI. Ambulatory diagnostic tools are often used in combination with tools that calculate patients' risk (the sensitivity and specificity of the test depend on pre-test probability). When ambulatory diagnosis is used, coexisting sleep disorders (eg, restless legs syndrome) are not excluded. Follow-up polysomnography may still be needed.

Adjunctive testing may include upper airway imaging, measurement of thyroid-stimulating hormone, and other tests as appropriate to assess chronic medical conditions associated with OSA.

Prognosis

Prognosis is excellent if effective treatment is instituted.

Untreated or unrecognized OSA leads to cognitive impairment as a result of sleeplessness, which, in turn, can lead to serious injury or death caused by accidents, especially motor vehicle crashes. Sleepy patients should be warned of the risk of driving, operating heavy machinery, or engaging in other activities during which sleep attacks would be hazardous.

Adverse effects of hypersomnolence, such as loss of employment and sexual dysfunction, can affect families considerably.

Long-term cardiovascular sequelae of untreated OSA include poorly controlled hypertension and heart failure.

In addition, perioperative complications, including cardiac arrest, have been attributed to OSA, probably because anesthesia can cause airway obstruction after a mechanical airway is removed. Patients should therefore inform their anesthesiologist of the diagnosis before undergoing surgery and should expect to receive continuous positive airway pressure (CPAP) when they receive preoperative drugs and during recovery.

Treatment

• Control of risk factors

• CPAP or oral appliances

• Possibly airway surgery for anatomic encroachment or intractable disease

The aim of treatment is to reduce episodes of hypoxia and sleep fragmentation; treatment is tailored to the patient and to the degree of impairment. Cure is defined as a resolution of symptoms with AHI reduction below a threshold, usually 10/h.

Treatment is directed first at risk factors and then at OSA itself. Specific treatments for OSA include CPAP, oral appliances, and airway surgery.

Control of risk factors: Initial treatment aims at optimal control of modifiable risk factors, including obesity, alcohol and sedative use, hypothyroidism, acromegaly, and other chronic disorders. Although modest weight loss (15%) may result in clinically meaningful improvement, weight loss is extremely difficult for most people, especially those who are fatigued or sleepy. Bariatric surgery reverses symptoms and improves AHI in 85% of morbidly obese (BMI > 40) patients.

CPAP: Nasal CPAP is the treatment of choice for most patients with OSA and subjective daytime sleepiness; adherence is lower in patients who do not experience sleepiness. CPAP improves upper airway patency by applying positive pressure to the collapsible upper airway segment. Effective pressures typically range from 3 to 15 cm H_2O. Disease severity does not correlate with pressure requirements. If clinical improvement is not apparent, pressure can be titrated during monitoring with repeat polysomnography. Regardless of improvement in the AHI, CPAP will reduce cognitive impairment and BP. If CPAP is withdrawn, symptoms recur over several days, though short interruptions of therapy for acute medical conditions are usually well tolerated. Duration of therapy is indefinite.

Failures of nasal CPAP are common because of limited patient adherence. Adverse effects include dryness and nasal irritation, which can be alleviated in some cases with the use of warm humidified air, and discomfort resulting from a poorly fitting mask.

CPAP can be augmented with inspiratory assistance (bilevel positive airway pressure) for patients with obesity-hypoventilation syndrome (see p. 57).

Oral appliances: Oral appliances are designed to advance the mandible or, at the very least, prevent retrusion with sleep. Some are also designed to pull the tongue forward. Use of these appliances to treat both snoring and OSA is gaining acceptance. Comparisons of appliances to CPAP show equivalence in mild to moderate OSA, but results of costeffectiveness studies are not available.

Airway surgery: Surgical correction of upper airway obstruction caused by enlarged tonsils and nasal polyps should be considered. Surgery for macroglossia or micrognathia is also an option. Surgery is a first-line treatment if anatomic encroachment is identified; otherwise, surgery is a second-tier approach.

Uvulopalatopharyngoplasty (UPPP) is the most commonly used procedure. It involves resection of submucosal tissue from the tonsillar pillars to the arytenoepiglottic folds, including resection of the adenoids, to enlarge the upper airway. Equivalence with CPAP was shown in one study using CPAP as a bridge to surgery, but the interventions have not been directly compared. UPPP may not be successful in patients who are morbidly obese or who have anatomic narrowing of the airway. Moreover, recognition of sleep apnea after UPPP is obscured because of a lack of snoring. Such silent obstructions may be as severe as apneic episodes before surgical intervention.

Adjunctive surgical procedures include midline glossectomy, hyoid advancement, and mandibulomaxillary advancement. The latter is often offered as a 2nd-stage procedure if UPPP is not curative. Studies of multistage approaches across centers in unselected patients are not available.

Tracheostomy is the most effective therapeutic maneuver for OSA but is done as a last resort. It bypasses the site of obstruction and is indicated for patients most severely affected (eg, those with cor pulmonale).

Laser-assisted uvuloplasty, uvular splints, and radiofrequency tissue ablation have been promoted as treatments for loud snoring in patients without OSA. Although they may transiently decrease snoring loudness, efficacy declines over months to years.

Adjunctive treatments: Adjunctive treatments are commonly used but have no proven role as first-line treatment.

Modafinil can be used for residual sleepiness in OSA in patients who are effectively using CPAP.

Supplemental O_2 improves blood oxygenation, but a beneficial clinical effect cannot be predicted. Also, O_2 may provoke respiratory acidosis and morning headache in some patients.

A number of drugs have been used to stimulate ventilatory drive (eg, tricyclic antidepressants, theophylline) but cannot be routinely advocated because of limited efficacy, a low therapeutic index, or both.

Nasal dilatory devices and throat sprays sold OTC for snoring have not been studied sufficiently to prove benefits for OSA.

Patient education and support: An informed patient and family are better able to cope with a treatment strategy, including tracheostomy. Patient support groups provide helpful information and effectively support timely treatment and follow-up.

Obstructive Sleep Apnea in Children

Obstructive sleep apnea (OSA) is episodes of partial or complete closure of the upper airway that occur during sleep and lead to breathing cessation. Symptoms include snoring and sometimes restless sleep, nocturnal sweating, and morning headache. Complications may include growth disturbance, cor pulmonale, pulmonary hypertension, and learning or behavioral disturbances. Diagnosis is by polysomnography. Treatment is usually adenotonsillectomy.

The prevalence of OSA in children is about 2%. The condition is underdiagnosed and can lead to serious sequelae.

Etiology

Risk factors for OSA in children include the following:

- Enlarged tonsils or adenoids
- Certain dental abnormalities (eg, large overbite)
- Obesity
- Craniofacial abnormalities (eg, micrognathia, retrognathia, midfacial hypoplasia, excessively angled skull base)
- Certain drugs (eg, sedatives, opioids)
- Mucopolysaccharidoses
- Disorders causing hypotonia or hypertonia (eg, Down syndrome, cerebral palsy, muscular dystrophies)
- Possibly genetic factors

Symptoms and Signs

Almost all affected children snore. Other sleep symptoms may include restless sleep, sweating at night, and observed apnea. Daytime symptoms may include nasal obstruction, mouth breathing, morning headache, and problems concentrating. Children may have nocturnal enuresis. Excessive daytime sleepiness is less common than among adults with OSA.

Complications of OSA may include cor pulmonale, pulmonary hypertension, growth disturbance, and problems with learning and behavior.

Examination may reveal no abnormalities or may show anatomic facial, nasal, or oral abnormalities contributing to obstruction, increase in the pulmonic component of the 2nd heart sound, or growth disturbance.

Diagnosis

• Polysomnography with end-tidal CO_2 monitoring

OSA is considered in children with snoring or risk factors. If symptoms of OSA are present, diagnostic testing is done; clinical criteria are not accurate. Diagnosis is by overnight polysomnography in a sleep laboratory that includes end-tidal CO_2 monitoring. The accuracy of home polysomnography is under evaluation. Although criteria for OSA in adults do not apply to children, experts disagree on what criteria should be used to diagnose OSA in children. Outcome data are lacking. However, OSA is generally considered present if polysomnography shows the following:

• > 1 apneic or > 2 hypopneic events/h (an event lasts > 2 breaths)

• End-tidal CO_2 > 50 mm Hg for > 10% total sleep time together with paradoxical respiration or snoring in patients without lung disorders

Patients with OSA are evaluated for cardiopulmonary complications with ECG and chest x-ray.

Treatment

• Adenotonsillectomy or correction of congenital micrognathia

• CPAP as 2nd-line therapy

Children who are otherwise healthy are treated with adenotonsillectomy, which is usually effective. Adenoidectomy alone is often ineffective. The risk of perioperative airway obstruction is higher among children with OSA than among children without OSA who undergo adenotonsillectomy; thus, close monitoring is important.

For children who are not otherwise healthy, who have complex anatomic abnormalities or genetic conditions altering respiratory control, or who have cardiopulmonary complications, a physician experienced in management of OSA in children should be consulted. Adenotonsillectomy may be effective or may provide some relief. Depending on the anatomic abnormality causing OSA, an alternate surgical procedure may be indicated (eg, uvulopalatopharyngoplasty, tongue or midface surgeries).

CPAP can be used for children who are not candidates for corrective surgery or who continue to have OSA after adenotonsillar surgery. Weight loss can decrease OSA severity in obese children and has other health benefits but is rarely sufficient treatment for OSA as monotherapy. Nocturnal O_2 supplementation may help prevent hypoxemia until definitive treatment can be accomplished. Corticosteroids and antibiotics are not usually indicated.

Central Sleep Apnea

Central sleep apnea (CSA) is a heterogeneous group of conditions characterized by changes in ventilatory drive without airway obstruction. Most of these conditions cause asymptomatic

changes in breathing pattern during sleep.

Etiology

Patients with CSA fall into 2 groups. One group presents with hypercapnia with decreased ventilatory drive. Causes include hypothyroidism and central lesions, such as brain stem infarctions, encephalitis, and Arnold-Chiari malformation. This type of CSA may also complicate neuromuscular diseases (eg, muscular dystrophy, amyotrophic lateral sclerosis, postpolio syndrome) and chest wall abnormalities (notably, kyphoscoliosis). The other group presents with eucapnia or hypocapnia with increased ventilatory drive but with sleep-induced apnea, periodic breathing, or both. Cheyne-Stokes breathing is a discrete pattern of this form of CSA thought to be caused by delays in circulation time that, in turn, cause a lag in recognition by respiratory centers of acidosis, hypoxia, or both (causing hyperpnea) and of alkalosis, hypocapnia, or both (causing apnea). High altitude is another cause of recurrent CSA manifesting with hypocapnia. Use of opioids can cause either hypercapneic or hypocapneic CSA.

Congenital central hypoventilation (a form of Ondine's curse) is a rare form of idiopathic CSA in neonates and may be associated with Hirschsprung's disease. A mutation in the *PHOX2* gene is responsible for 80 to 90% of cases. This mutation produces variable phenotypes, and clinically evident cases are inherited in a dominant pattern.

Symptoms and Signs

CSA is usually asymptomatic and is detected by caretakers or bed partners who notice long respiratory pauses, shallow breaths, or restless sleep. Patients with hypercapnic forms may experience daytime somnolence, lethargy, and morning headache.

Diagnosis

Diagnosis is suspected on the basis of history and is confirmed by polysomnography. However, testing may not be necessary if CSA causes no symptoms or is clearly related to an identifiable disorder. To diagnose causes of CSA, brain or brain stem imaging may be indicated.

Treatment

• Supportive care

Primary treatment is optimal management of underlying conditions and avoidance of opioids and other sedatives. Secondary treatment of symptomatic patients can be a trial of supplemental O_2 or, in patients with hypercapnic CSA who have symptoms despite other treatments, noninvasive continuous or bi-level positive airway pressure. Acetazolamide is effective in CSA caused by high altitude. Phrenic nerve pacing is an option for children > 2 yr with congenital central hypoventilation syndrome.

Chapter 194. Pulmonary Embolism

Introduction

Pulmonary embolism (PE) is the occlusion of ≥ 1 pulmonary arteries by thrombi that originate elsewhere, typically in the large veins of the lower extremities or pelvis. Risk factors are conditions that impair venous return, conditions that cause endothelial injury or dysfunction, and underlying hypercoagulable states. Symptoms are nonspecific and include dyspnea, pleuritic chest pain, cough, and, in severe cases, syncope or cardiorespiratory arrest. Signs are also nonspecific and may include tachypnea, tachycardia, hypotension, and a loud pulmonic component of the 2nd heart sound. Diagnosis is based on a CT angiogram, ventilation/perfusion scan, or a pulmonary arteriogram. Treatment is with anticoagulants and, sometimes, clot dissolution with thrombolytics or surgical removal. Preventive measures include anticoagulants and sometimes insertion of an inferior vena caval filter.

PE affects an estimated 117 people per 100,000 person years, resulting in about 350,000 cases yearly, and causes up to 85,000 deaths/yr. PE affects mainly adults.

Etiology

Nearly all PEs arise from thrombi in the lower extremity or pelvic veins (deep venous thrombosis [DVT] —see p. 2224). Thrombi in either the lower extremity or pelvic veins may be occult. Risk of embolization is higher with thrombi proximal to the calf veins. Thromboemboli can also originate in upper extremity veins (associated with central venous catheters) or from right-sided cardiac chambers. Risk factors for DVT and PE are similar in children and adults and include conditions that impair venous return, conditions that cause endothelial injury or dysfunction, and underlying hypercoagulability disorders (see Table 194-1). Bed rest and confinement without walking, even for a few hours, are common precipitators.

Pathophysiology

Once DVT develops, clots may dislodge and travel through the venous system and right side of the heart to lodge in the pulmonary arteries, where they partially or completely occlude one or more vessels. The consequences depend on the size and number of emboli, the pulmonary reaction, the underlying condition of the lungs, and the ability of the body's intrinsic thrombolytic system to dissolve the clots.

[**Table 194-1.** Risk Factors for Deep Venous Thrombosis and Pulmonary Embolism]

Small emboli may have no acute physiologic effects; many begin to lyse immediately and resolve within hours or days. Larger emboli can cause a reflex increase in ventilation (tachypnea), hypoxemia due to ventilation/perfusion (V/Q) mismatch, shunting and low mixed venous O_2 content as a result of low cardiac output, atelectasis due to alveolar hypocapnia and abnormalities in surfactant, and an increase in pulmonary vascular resistance caused by mechanical obstruction and vasoconstriction. Endogenous lysis reduces most emboli, even those of moderate size, without treatment, and physiologic alterations decrease over hours or days. Some emboli resist lysis and may organize and persist. Occasionally, chronic residual obstruction leads to pulmonary hypertension (chronic thromboembolic pulmonary hypertension) that may develop over years and result in chronic right heart failure. When large emboli occlude major arteries, or when many small emboli occlude > 50% of the distal arterial system, right ventricular pressure increases, causing acute right ventricular failure, failure with shock (massive PE), or sudden death in severe cases. Risk factors for death include age > 70 yr, cancer, and COPD. The risk of death depends on the degree and rate of rise of right-sided pressures and on the patient's underlying cardiopulmonary status; higher pressures more commonly occur among patients with preexisting cardiopulmonary disease. Otherwise healthy patients may survive a PE that occludes > 50% of the pulmonary vascular bed.

Pulmonary infarction occurs in < 10% of patients diagnosed with PE. This low rate has been attributed to the dual blood supply to the lung (ie, bronchial and pulmonary).

PE can also arise from nonthrombotic sources (see Sidebar 194-1).

Symptoms and Signs

Most PEs are small, physiologically insignificant, and asymptomatic. Even when present, symptoms are nonspecific and vary in frequency and intensity, depending on the extent of pulmonary vascular occlusion and preexisting cardiopulmonary function.

Larger emboli cause acute dyspnea, pleuritic chest pain, or both. Dyspnea may be intermittent or occur only with exercise. Less common symptoms include cough and hemoptysis. The first symptom in an elderly patient may be altered mental status. Massive PE manifests with hypotension, tachycardia, syncope, or cardiac arrest.

The most common signs of PE are tachycardia and tachypnea. Less commonly, patients have hypotension, a loud 2nd heart sound (S_2) due to a loud pulmonic component (P_2), and crackles or wheezing. In the presence of right ventricular failure, distended internal jugular veins and a right ventricular heave may be evident, and right ventricular gallop (3rd and 4th heart sounds [S_3 and S_4]), with or without tricuspid regurgitation, may be audible. Fever can occur; DVT and PE are often overlooked causes of fever.

Pulmonary infarction is typically characterized by chest pain (mainly pleuritic), fever, and, occasionally, hemoptysis. Chronic thromboembolic pulmonary hypertension causes symptoms and signs of right heart failure, including exertional dyspnea, easy fatigue, and peripheral edema that develops over months to years.

Diagnosis

• High index of suspicion

• Assessment of pretest probability (based on clinical findings, pulse oximetry, and chest x-ray)

• Subsequent testing based on pre-test probability

Diagnosis is challenging, because symptoms and signs are nonspecific and diagnostic tests have imperfect diagnostic accuracy or are invasive. Most important is to include PE in the differential diagnosis when nonspecific symptoms, such as dyspnea, pleuritic chest pain, fever, hemoptysis, and cough, are encountered. Thus, PE should be considered in the differential diagnosis of patients suspected of having such conditions as cardiac ischemia, heart failure, COPD exacerbation, pneumothorax, pneumonia, sepsis, acute chest syndrome (in patients with sickle cell disease), and acute anxiety with hyperventilation. PE also should be considered in any elderly patient with tachypnea and altered mental status.

Initial evaluation should include pulse oximetry and chest x-ray. Some experts also recommend ECG, ABG, or both, sometimes to exclude other diagnoses (eg, acute MI). The chest x-ray usually is nonspecific but may show atelectasis, focal infiltrates, an elevated hemidiaphragm, or a pleural effusion. The classic findings of focal loss of vascular markings (Westermark's sign), a peripheral wedge-shaped density (Hampton's hump), or enlargement of the right descending pulmonary artery (Palla's sign) are suggestive but uncommon (ie, insensitive) and have an unknown specificity. Chest x-ray can also help exclude pneumonia.

Pulse oximetry provides a quick way to assess oxygenation; hypoxemia is one sign of PE, and it requires further evaluation. ABG measurement may show an increased alveolar to arterial oxygen (A-a) gradient (see p. 1856) or hypocapnia; one or both of these tests are moderately sensitive for PE but are not specific. ABG testing should be considered particularly for patients with dyspnea or tachypnea who do not have hypoxemia detected with pulse oximetry.

Sidebar 194-1 Nonthrombotic Pulmonary Embolism

PE caused by various nonthrombotic sources causes clinical syndromes that differ from those caused by thrombotic PE. Treatment of all includes supportive measures.

Air embolism is caused by introduction of large amounts of air into systemic veins or into the right side of the heart, which then move to the pulmonary arterial system. Pulmonary outflow tract obstruction may occur, which can be rapidly fatal. Causes include surgery, blunt trauma, defective or uncapped venous catheters, and errors occurring during the insertion or removal of central venous catheters. Treatment includes placement of patient in left lateral decubitus position, preferably in the Trendelenburg position (ie, head lower than feet), to trap air in the apex of the right ventricle and thus prevent brain embolism and supportive measures. Rapid decompression after underwater diving may cause microbubble formation in the pulmonary circulation, a different problem, which results in endothelial damage, hypoxemia, and diffuse infiltrates (see p. 3285).

Fat embolism is caused by introduction of fat or bone marrow particles into the systemic venous system and then into pulmonary arteries. Causes include fractures of long bones, orthopedic procedures, microvascular occlusion or necrosis of bone marrow in patients with sickle cell crisis, and, rarely, toxic modification of native or parenteral serum lipids. Fat embolism causes a pulmonary syndrome similar to acute respiratory distress syndrome (ARDS), with severe hypoxemia of rapid onset often accompanied by neurologic changes and a petechial rash. Early splinting of fractures of long bones and operative rather than external fixation are thought to help prevent fat embolism.

Amniotic fluid embolism is a rare syndrome caused by introduction of amniotic fluid into the maternal venous and then pulmonary arterial system. The syndrome occurs around the time of labor (see p. 2678) or, even less often, during prepartum uterine manipulations. Patients can have cardiac and respiratory distress due to anaphylaxis, vasoconstriction causing acute severe pulmonary hypertension, and direct pulmonary microvascular toxicity with hypoxemia and pulmonary infiltrates.

Septic embolism occurs when infected material embolizes to the lung. Causes include IV drug use, right-sided infective endocarditis, and septic thrombophlebitis. Septic embolism causes symptoms and signs of pneumonia or sepsis. Initially, nodular opacities appear on the chest x-ray; the appearance may progress to peripheral infiltrates, and emboli may cavitate (particularly emboli caused by *Staphylococcus aureus*). Treatment includes that of the underlying infection.

Foreign body embolism caused by introduction of particulate matter into the pulmonary arterial system, usually by IV injection of inorganic substances, such as talc by heroin users or elemental mercury by patients with mental disorders. Focal pulmonary infiltrates may result.

Tumor embolism is a rare complication of cancer (usually adenocarcinoma) in which neoplastic cells from an organ enter the systemic venous and pulmonary arterial system, where they lodge, proliferate, and obstruct flow. Patients typically present with dyspnea and pleuritic chest pain and signs of cor pulmonale that develop over weeks to months. Diagnosis, which is suggested by micronodules or diffuse pulmonary infiltrates on chest x-ray, can be confirmed by biopsy or occasionally by cytologic aspiration and histologic study of pulmonary capillary blood.

ECG most often shows tachycardia and various ST-T wave abnormalities, which are not specific for PE (see Fig. 194-1). An $S_1Q_3T_3$ or a new right bundle branch block may indicate the effect of abrupt rise in right ventricular pressure on right ventricular conduction; these findings are moderately specific but insensitive, occurring in only about 5% of patients. Right axis deviation (R > S in V_1) and P-pulmonale may be present. T-wave inversion in leads V_1 to V_4 also occurs.

Clinical probability: Clinical probability of PE can be assessed by combining ECG and chest x-ray findings with findings from the history and physical examination (see Table 194-2). Judgment of whether PE is more likely than an alternate diagnosis is somewhat subjective. PE should probably be considered more likely if ≥ 1 of its symptoms and signs, particularly dyspnea,

hemoptysis, tachycardia, or hypoxemia, cannot be explained clinically or by chest x-ray results. Patients with a low clinical

[Fig. 194-1. An ECG in pulmonary embolism.]

[Table 194-2. Clinical Prediction Rule for Diagnosing Pulmonary Embolism]

probability of PE may need only minimal additional testing. Patients with an intermediate clinical probability are likely to need more additional testing. Patients with a high probability may be candidates for immediate treatment pending confirmation with additional testing. Patients do not need any testing for PE if the clinical probability is very low and there are no objective cardiopulmonary abnormalities.

Noninvasive testing: Noninvasive testing typically can be obtained more quickly and carries less morbidity than invasive testing. Tests most useful for diagnosing or excluding PE are D-dimer testing, V/Q scanning, duplex ultrasonography, CT angiography (helical CT with IV contrast), and echocardiography.

There is no universally accepted algorithm for the best choice and sequence of tests, but one common approach is

- Screening with D-dimer testing
- Lower extremity ultrasonography (which exposes the patient to no ionizing radiation) when the D-dimer result is positive
- CT angiography (or V/Q scanning) if duplex ultrasonography is negative

Patients with a moderate to high probability of disease based on clinical criteria who have low- or intermediate-probability V/Q scans usually require pulmonary arteriography or CT angiography to make or exclude the diagnosis. Lower-extremity ultrasonography is not diagnostic for PE, but a study that reveals thrombus formation establishes the need for anticoagulation and obviates the need for further diagnostic testing. A negative result on ultrasonography does not negate the need for additional studies. D-Dimer measurements, ECG, ABG measurements, chest x-ray, and echocardiography are adjunctive tests; positive results of these tests lack sufficient specificity to be diagnostic alone.

D-Dimer is a by-product of intrinsic fibrinolysis; thus, elevated levels occur in the presence of a recent thrombus. However, elevated levels are not specific for venous thrombus because many patients without DVT or PE also have elevated levels. More importantly, absence of elevated levels suggests the absence of recent thrombus because the test is sensitive; > 95% of patients with DVT or PE have elevated levels. Thus, a low D-dimer level has a negative predictive value of > 95%, making such a result sufficiently reliable for excluding the diagnosis of PE in routine practice among patients with a low or moderate pre-test probability.

V/Q scans detect areas of lung that are ventilated but not perfused, as occurs in PE; results are reported as low, intermediate, or high probability of PE based on patterns of V/Q mismatch. A completely normal scan excludes PE with nearly 100% accuracy, but a low probability scan still carries a 15% likelihood of PE. Perfusion deficits may occur in many other lung conditions, including pleural effusion, chest mass, pulmonary hypertension, pneumonia, and COPD. With an intermediate probability scan, there is a 30 to 40% probability of PE; with a high probability scan, there is an 80 to 90% probability of PE.

Duplex ultrasonography is a safe, noninvasive, portable technique for detecting lower extremity (primarily femoral vein) thrombi. A clot can be detected by visualizing the lining of the vein, by showing incompressibility of the vein, or by showing reduced flow by Doppler ultrasonography. The test has a sensitivity of > 90% and a specificity of > 95% for thrombus. It cannot reliably detect a clot in calf or iliac veins. Absence of thrombi in the femoral veins does not exclude the possibility of thrombus from other sources, but patients with negative results on Doppler duplex ultrasonography have > 95% event-free survival, because thrombi from other sources are so much less common.

CT angiography is an alternative to V/Q scanning and pulmonary arteriography in most settings because

it is fast, available, and noninvasive and gives more information about other lung pathology. However, patients must be able to hold their breath for several seconds. The sensitivity of CT angiography is highest for PE in lobar and segmental vessels and lowest for emboli in smaller subsegmental vessels (about 30% of all PEs) and thus is less sensitive than perfusion scans. In studies done using older scanners, overall sensitivities range from 53 to 100%; values are at the lower end of the range for subsegmental vessels. Specificities range from 81 to 100%. A positive scan may be diagnostic of PE, but a negative scan does not necessarily exclude subsegmental disease, though the clinical significance of emboli in smaller subsegmental vessels remains to be determined. Newer multidetector scans are more sensitive (about 83%) and are specific (about 96%) overall. Magnetic resonance angiography (MRA) is an alternative to CT angiography for patients who cannot tolerate contrast agents and for pregnant patients.

Echocardiography as a diagnostic test for PE is controversial. Its sensitivity is > 80% for detecting right ventricular dysfunction (eg, dilation and hypokinesis, which occur when pulmonary artery pressure exceeds 40 mm Hg). Right ventricular dysfunction is a useful measure of hemodynamic severity in acute PE, but dysfunction is present in several disorders, including COPD, heart failure, and sleep apnea, and is therefore a nonspecific finding. Estimation of pulmonary artery systolic pressure using Doppler flow signals gives additional useful information about the severity of acute PE. Absence of right ventricular dysfunction or pulmonary hypertension makes the diagnosis of a large PE unlikely but does not exclude the diagnosis of a smaller one.

Cardiac marker testing is evolving as a useful means of stratifying mortality risk in patients with acute PE. Elevated troponin levels can signify right ventricular strain. Elevated brain natriuretic peptide (BNP) and pro-BNP levels are not helpful, but low levels appear to signify good prognosis. The clinical role of these tests remains to be determined, because they are not specific for right ventricular strain or for PE.

Patients with PE and no known risk factors should be considered for hypercoagulability testing (see p. 973), especially if they are < 35 yr, have recurrent PE, or have a positive family history.

Invasive tests: Pulmonary arteriography is indicated

• When the pre-test probability of PE is moderate or high and noninvasive tests are inconclusive

• When the need to make or exclude the diagnosis is urgent, such as in an acutely ill patient

• When anticoagulation is contraindicated

• When chronic thromboembolic pulmonary hypertension is suspected

Pulmonary arteriography is still the most accurate test for diagnosing PE, but it is needed much less often because of the sensitivity of ultrasonography and CT angiography. A pulmonary arteriogram that reveals intraluminal filling defects or abrupt cutoff of flow is positive. Findings suggestive but not diagnostic of PE include partial occlusion of pulmonary arterial branches with increased proximal and decreased distal caliber, oligemic zones, and persistence of dye in the proximal artery during the late (venous) phase of the pulmonary arteriogram. In lung segments with obstructed arteries, venous filling with contrast medium is delayed or absent.

Prognosis

An estimated 10% of patients with PE die within 1 h. Of those patients who survive the first hour, only about 30% are diagnosed and receive treatment; > 95% of these patients survive. Thus, most patients with PE are never diagnosed; it is in such patients that most mortality from PE occurs. The best prospects for reducing mortality lie in improving diagnosis, not in improving treatment. Patients with chronic thromboembolic disease represent a tiny fraction of patients with PE who survive. Anticoagulant therapy reduces the rate of recurrence of PE to about 5% in all patients.

Treatment

- Anticoagulation
- Inferior vena cava filter placement when anticoagulation contraindicated or ineffective
- Clot elimination (eg, thrombolytic therapy, embolectomy) for massive emboli

Initial treatment of PE is O_2 for hypoxemia and IV 0.9% saline and vasopressors for hypotension and anticoagulation. All patients with strongly suspected or confirmed PE should be hospitalized and, ideally, should also be continually monitored for life-threatening cardiovascular complications in the first 24 to 48 h. Clot elimination should be considered in patients with massive PE at the time of diagnosis.

Clot elimination: Clot elimination by means of embolectomy or dissolution by IV thrombolytic therapy should be considered for hypotensive patients. It may also be indicated for patients with clinical, ECG, or echocardiographic evidence of right ventricular overload or failure, but data supporting use in these patients are scarce and not definitive, and controlled prospective studies are unlikely to be done.

Embolectomy is reserved for patients with PE who are hypotensive despite supportive measures (persistent systolic BP ≤ 90 mm Hg after fluid therapy and O_2 or if pressor therapy is required) or on the verge of cardiac or respiratory arrest. Surgical embolectomy appears to improve survival in patients with massive PE but is not widely available. Catheter-based embolectomy can be done by some interventional radiologists. The decision to proceed with embolectomy and the choice of technique depend on local resources and expertise.

Thrombolytic therapy with tissue plasminogen activator (tPA), streptokinase, or urokinase offers a noninvasive way to rapidly restore pulmonary blood flow but is controversial because long-term benefits do not clearly outweigh the risk of hemorrhage. In patients with submassive PE (ie, who are normotensive but have right ventricular dysfunction), thrombolytics speed the resolution of radiographic abnormalities and the return of hemodynamic function (heart rate and right ventricular function) and prevent cardiopulmonary deterioration but have not been shown to improve survival. Some experts recommend thrombolytics for patients with submassive PE suspected on the basis of echocardiographic evidence of proximal pulmonary artery (large) embolism or of right ventricular dysfunction due to either PE or preexisting disease. Others reserve thrombolytic therapy for patients with massive PE.

Absolute contraindications to thrombolytics include prior hemorrhagic stroke, ischemic stroke within 1 yr, active external or internal bleeding from any source, intracranial injury or surgery within 2 mo, intracranial tumor, GI bleeding within 6 mo, and CPR.

Relative contraindications include recent surgery (≤ 10 days), hemorrhagic diathesis (as in hepatic insufficiency), pregnancy, current use of anticoagulants and an INR > 2, punctures of large noncompressible veins (eg, subclavian or internal jugular veins), recent femoral artery catheterization (eg, ≤ 10 days), peptic ulcer disease or other conditions that increase the risk of bleeding, and severe hypertension (systolic BP > 180 or diastolic BP > 110 mm Hg).

Options for thrombolysis include streptokinase, urokinase, and alteplase (recombinant tPA). Standard IV regimens are streptokinase 250,000 units over 30 min followed by continuous infusion of 100,000 units/h for 24 h; urokinase 4400 units/kg over 10 min followed by 4400 units/kg/h for 12 h; or alteplase 100 mg continuous infusion over 2 h followed by an additional 40 mg over another 4 h (10 mg/h) if clinical presentation and repeat pulmonary angiogram suggest failure of clot lysis and initial dosing does not cause bleeding. Although no drug has proved superior to the others, streptokinase is now rarely used because of the risk of allergic and pyrogenic reactions and because administration requires constant infusion for > 24 h.

An initial loading dose of heparin should be given concurrently, but the activated PTT should be allowed to fall to 1.5 to 2.5 times the baseline value before beginning continuous heparin infusion. Direct delivery of thrombolytics to the clot via a pulmonary artery catheter is occasionally used for patients with massive PE or for those with relative contraindications to systemic thrombolytics, but this approach does not prevent systemic thrombolysis. Bleeding, if it occurs, can be reversed with cryoprecipitate or fresh frozen plasma. Accessible vascular access sites can be compressed.

Anticoagulation: Because embolization rarely involves an entire venous thrombus, anticoagulation is required acutely to prevent residual clot from extending and embolizing. Patients in whom anticoagulants are contraindicated or those who have thromboemboli despite therapeutic anticoagulation should have placement of a removable percutaneous inferior vena cava filter.

Heparin, either unfractionated or low molecular weight, is the mainstay of treatment of acute DVT and PE and should be given immediately on diagnosis or sooner if clinical suspicion is high and if the patient has cardiorespiratory compromise. Inadequate anticoagulation in the first 24 h is linked to increased risk of recurrent PE for up to 3 mo. Heparin accelerates the action of antithrombin III, an inhibitor of coagulation factors; unfractionated heparin also has antithrombin III-mediated anti-inflammatory properties, which may facilitate clot organization and reduce thrombophlebitis. Unfractionated heparin should be given as a bolus and infusion by protocol (see Fig. 194-2) to achieve an activated PTT 1.5 to 2.5 times that of normal control. Subcutaneous low molecular weight heparin (LMWH) is as effective as unfractionated heparin and may cause less thrombocytopenia (for dosing, see Table 194-3). Because of its long half-life, it is useful in outpatient treatment (usually restricted to patients with DVT without PE) and to facilitate earlier discharge of patients who have not achieved therapeutic anticoagulation with warfarin.

Adverse effects of all heparins include the following:

• Bleeding

• Thrombocytopenia

• Urticaria

• Thrombosis or anaphylaxis (rarely)

Long-term heparin administration may cause the following:

• Hypokalemia

• Liver enzyme elevations

• Osteoporosis

Before use, patients should be screened for GI bleeding by testing for occult blood in stool. During treatment, they should be monitored for bleeding with serial CBCs and tests for occult blood in stool. Bleeding caused by over-heparinization can be stopped with a maximum of 50 mg of protamine per 5000 units unfractionated heparin infused over 15 to 30 min (or 1 mg in 20 mL normal saline infused over 10 to 20 min for LMWH, though the precise dose is undefined because protamine only partially neutralizes LMWH inactivation of factor Xa). Treatment with heparin or LMWH is continued until full anticoagulation has been achieved with oral warfarin. The use of LMWH in long-term anticoagulation

[**Fig. 194-2.** Weight-based heparin dosing.]

after acute PE has not been studied but will likely be limited by cost and ease of administration compared with oral warfarin.

Warfarin is the oral drug of choice for long-term anticoagulation in all patients except pregnant women and patients with new or worsening venous thromboembolism during warfarin treatment. Five to 10 mg po once/day should be started when the PTT has been consistently ≥ 1.5 to 2.0 times control values. The therapeutic goal with warfarin is usually an INR of 2 to 3.

Physicians prescribing warfarin should be wary of drug interactions (see Table 194-4), including interactions with nonprescription drugs and medicinal herbs. Patients with

temporary risk factors for DVT or PE (eg, fracture or surgery) can stop the drug after 3 to 6 mo. Patients with permanent risk factors (eg, hypercoagulability), no known risk factors, or recurrent DVT or PE should take warfarin for at least 6 mo and possibly for life unless complications of therapy intervene. In low-risk patients, low-intensity warfarin (to maintain

[**Table 194-3.** Some Low Molecular Weight Heparin* Options in Thromboembolic Disease]

INR at 1.5 to 2.0) may be safe and effective for at least 2 to 4 yr, but this regimen requires further proof of safety before it can be routinely recommended.

Bleeding is the most common complication of warfarin treatment; patients > 65 and those with comorbidities (especially diabetes, recent MI, Hct < 30%, or creatinine > 1.5 mg/dL) and a history of stroke or GI bleeding seem to be at greatest risk. Bleeding can be reversed with 2.5 to 10 mg of vitamin K sc or po and, in an emergency, with fresh frozen plasma. Vitamin K may cause flushing, local pain, and, rarely, anaphylaxis.

[**Table 194-4.** Drug, Herbal Preparation, and Food Interactions with Warfarin]

Prevention

Prevention of PE means prevention of DVT; the need depends on the patient's risks. Bedbound patients and patients undergoing surgical, especially orthopedic, procedures especially benefit, and most of these patients can be identified before a thrombus forms (see Table 194-5). Preventive measures include low-dose unfractionated heparin (LDUH), LMWH, warfarin, newer anticoagulants, compression devices, and elastic compression stockings. Choice of drug or device depends on whether patients are undergoing surgery (and the type of surgery), duration of treatment, contraindications, relative costs, and ease of use.

Drugs: LDUH is given in doses of 5000 units sc 2 h preoperatively and q 8 to 12 h thereafter for 7 to 10 days or until the patient is fully ambulatory. Immobilized patients not

[**Table 194-5.** Risk of Deep Venous Thrombosis and Pulmonary Embolism in Surgical Patients]

undergoing surgery should receive 5000 units sc q 12 h until they are ambulatory.

LMWH dosing depends on the drug and on whether the drug is being used for prevention or treatment; enoxaparin, dalteparin, and tinzaparin are equally effective as LDUH for preventing DVT and PE.

Fondaparinux 2.5 mg sc once/day is as effective as LMWH for orthopedic surgery and in some other settings. It is a selective factor Xa inhibitor.

Warfarin is usually effective and safe at a dose of 2 to 5 mg po once/day or at a dose adjusted to maintain an INR of 2 to 3.

Newer anticoagulants, including hirudin, a subcutaneous direct thrombin inhibitor, and lepirudin, a recombinant hirudin, have demonstrated efficacy in DVT and PE prevention but warrant further study to determine their cost-effectiveness and safety relative to heparins and warfarin (also see Tables 194-3 and 194-6).

Aspirin is better than placebo but worse than all other available drugs for preventing DVT and PE.

Devices: Inferior vena cava filters, intermittent pneumatic compression, and graded elastic compression stockings may be used in combination with drugs to prevent PE.

An **inferior vena cava filter** (IVCF) may help prevent PE in patients with lower extremity DVT, but IVCF placement may risk long-term complications. Benefits outweigh risks if a 2nd PE is predicted to be life threatening; however, risks outweigh benefits in most patients. A filter is most commonly

[Table 194-6. Some Anticoagulation Options Other Than Heparin in Thromboembolic Disease]

placed in patients with contraindications to anticoagulation, with recurrent DVT (or emboli) despite adequate anticoagulation, after embolectomy, and, occasionally, in those whose marginal cardiopulmonary function raises concern for their ability to tolerate additional small emboli. Because venous collaterals can develop, providing a pathway for emboli to circumvent the IVCF, patients with recurrent DVT or nonmodifiable risk factors for DVT may still require anticoagulation. An IVCF is placed in the inferior vena cava just below the renal veins via catheterization of an internal jugular or femoral vein. Some IVCFs are removable. Occasionally, a filter dislodges, may migrate up the venous bed, even to the heart, and needs to be removed or replaced. A filter can also become clotted, causing bilateral lower extremity venous congestion (including acute phlegmasia cerulea dolens), lower body ischemia, and acute renal failure. Filter clotting requires careful evaluation for complications and risks of intervention.

Intermittent pneumatic compression (IPC) provides rhythmic external compression to the legs or to the legs and thighs. It is more effective for preventing calf than proximal DVT and thus is considered inadequate after hip or knee surgery. IPC is contraindicated in obese patients and can theoretically trigger PE in immobilized patients who have developed occult DVT while not undergoing preventive treatment.

Graded elastic compression stockings have largely been abandoned in favor of external pneumatic leg compression.

Choice of prevention: For surgical procedures with a high incidence of venous thromboembolism, such as hip and lower extremity orthopedic surgery, LDUH q 8 h, LMWH, or adjusted-dose warfarin is recommended. For total knee replacement, risk reductions provided by LMWH and IPC are comparable but not optimal, so both should be used. The regimens for orthopedic surgery may be initiated preoperatively and should be continued for at least 7 days postoperatively. In selected patients at very high risk of both venous thromboembolism and bleeding, placement of an IVCF is an option for prophylaxis.

A high risk of venous thromboembolism also occurs in patients undergoing elective neurosurgery and those with acute spinal cord injury and multiple trauma. Although physical methods (IPC, elastic stockings) have been used in neurosurgical patients because of concern about intracranial bleeding, LMWH appears to be an acceptable alternative. The combination of IPC and LMWH may be more effective than either alone in high-risk patients. Limited data support the combination of IPC, elastic compression stockings, and LMWH in patients with spinal cord injury or in multiple trauma. For very high-risk patients, an IVCF may be considered.

The most common nonsurgical conditions in which DVT prophylaxis is indicated are acute MI and ischemic stroke. For MI patients, LDUH is effective; IPC, elastic compression stockings, or both may be used when anticoagulants are contraindicated. For stroke patients, LDUH or LMWH can be used; IPC, elastic compression stockings, or both may be beneficial.

Recommendations for some other nonsurgical conditions include LDUH for patients with heart failure; adjusted-dose warfarin (INR 1.3 to 1.9) for patients with metastatic breast cancer; and warfarin 1 mg/day for cancer patients with an indwelling central venous catheter.

Chapter 195. Acute Bronchitis

Acute bronchitis is inflammation of the upper airways, commonly following a URI. The cause is usually a viral infection, though it is sometimes a bacterial infection; the pathogen is rarely identified. The most common symptom is cough, with or without fever, and possibly sputum production. In patients with COPD, hemoptysis, burning chest pain, and hypoxemia may also occur. Diagnosis is based on clinical findings. Treatment is supportive; antibiotics are necessary only for selected patients with chronic lung disease. Prognosis is excellent in patients without lung disease, but in patients with COPD, acute respiratory failure may result.

Acute bronchitis is frequently a component of a URI caused by rhinovirus, parainfluenza, influenza A or B, respiratory syncytial virus, coronavirus, or human metapneumovirus. Less common causes may be *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Chlamydia pneumoniae*. Patients at risk include those who smoke and those with COPD or other diseases that impair bronchial clearance mechanisms, such as cystic fibrosis or conditions leading to bronchiectasis (see p. 1939).

Symptoms and Signs

Symptoms are a nonproductive or minimally productive cough accompanied or preceded by URI symptoms. Subjective dyspnea results from chest pain or tightness with breathing, not from hypoxia, except in patients with underlying lung disease. Signs are often absent but may include scattered rhonchi and wheezing. Sputum may be clear, purulent, or, occasionally, bloody. Sputum characteristics do not correspond with a particular etiology (ie, viral vs bacterial). Mild fever may be present, but high or prolonged fever is unusual and suggests influenza or pneumonia.

On resolution, cough is the last symptom to subside and often takes several weeks or even longer to do so.

Diagnosis

• Clinical evaluation

• Sometimes chest x-ray

Diagnosis is based on clinical presentation. Chest x-ray is necessary only if findings suggest pneumonia (eg, abnormal vital signs, crackles, signs of consolidation, hypoxemia). Elderly patients are the occasional exception. They may require chest x-ray for productive cough and fever in the absence of auscultatory findings (particularly if there is a history of COPD or another lung disorder).

Sputum Gram stain and culture usually have no role.

Cough resolves within 2 wk in 75% of patients. Patients with persistent cough should undergo a chest x-ray. Evaluation for pertussis, with a culture from nasopharyngeal secretions, and noninfectious etiologies, such as postnasal drip, allergic rhinitis, and coughvariant asthma, may be needed.

Treatment

• Symptom relief (acetaminophen, hydration, possibly antitussives)

• Inhaled β-agonist or anticholinergic for wheezing

• Sometimes oral antibiotics for patients with COPD

Acute bronchitis in otherwise healthy patients is a major reason that antibiotics are overused. Nearly all patients require only symptomatic treatment, such as acetaminophen and hydration. Antitussives should be used only if the cough is interfering with sleep (see p. 1831). Patients with wheezing may benefit from an inhaled β_2-agonist (eg, albuterol) or an anticholinergic (eg, ipratropium) for ≤ 7 days. If cough persists

for > 2 wk because of airway irritation, some patients benefit from a few days of inhaled corticosteroids. Oral antibiotics are typically not used except in patients with pertussis or in patients with COPD who have at least 2 of the following:

- Increased cough
- Increased dyspnea
- Increase in sputum purulence

Drugs include amoxicillin 500 mg po tid for 7 days, doxycycline 100 mg po bid for 7 days, azithromycin 500 mg po once/day for 4 days, or trimethoprim/sulfamethoxazole 160/800 mg po bid for 7 days.

Chapter 196. Pneumonia

Introduction

(See also Neonatal Pneumonia on p. 2832.)

Pneumonia is acute inflammation of the lungs caused by infection. Initial diagnosis is usually based on chest x-ray. Causes, symptoms, treatment, preventive measures, and prognosis differ depending on whether the infection is bacterial, viral, fungal, or parasitic; whether it is acquired in the community, hospital, or nursing home; and whether it develops in a patient who is immunocompetent or immunocompromised.

An estimated 2 to 3 million people in the US develop pneumonia each year, of whom about 45,000 die. Pneumonia is the most common fatal hospital-acquired infection and the most common overall cause of death in developing countries.

Bacteria are the most common cause of pneumonia in adults > 30 yr, *Streptococcus pneumoniae* infection being the most common pathogen in all age groups, settings, and geographic regions. However, pathogens of every sort, from viruses to parasites, cause pneumonia.

The airways and lungs are constantly exposed to pathogens in the external environment; the upper airways and oropharynx in particular are colonized with so-called normal flora rendered harmless by host defenses. Infection develops when pathogens that are inhaled or aspirated or reach the lungs via the bloodstream or contiguous spread overcome multiple host defenses.

Upper airway defenses include salivary IgA, proteases, and lysozymes; growth inhibitors produced by normal flora; and fibronectin, which coats the mucosa and inhibits adherence. Nonspecific lower airway defenses include cough, mucociliary clearance, and airway angulation preventing infection in airspaces. Specific lower airway defenses include various pathogen-specific immune mechanisms, including IgA and IgG opsonization, anti-inflammatory effects of surfactant, phagocytosis by alveolar macrophages, and T-cell-mediated immune responses. These mechanisms protect most people against infection. But numerous conditions alter normal flora (eg, systemic illness, undernutrition, hospital or nursing home exposure, antibiotic exposure) or impair these defenses (eg, cigarette smoking, nasogastric or endotracheal intubation). Pathogens that then reach airspaces can multiply and cause pneumonia.

Specific pathogens causing pneumonia cannot be found in < 50% of patients, even with extensive diagnostic investigation. But because pathogens and outcomes tend to be similar by setting and host risk factors, pneumonias can be categorized as

- Community-acquired
- Hospital-acquired (including ventilator-acquired and postoperative)
- Nursing home-acquired
- Occurring in immunocompromised people

These categorizations allow treatment to be selected empirically.

The term interstitial pneumonia refers to various unrelated conditions of varied and sometimes unknown causes characterized by inflammation and fibrosis of the pulmonary interstitium (see p. 1945).

Community-Acquired Pneumonia

Community-acquired pneumonia develops in people with limited or no contact with medical institutions or settings. The most commonly identified pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical organisms (ie, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella* sp). Symptoms and signs are fever, cough, pleuritic chest

pain, dyspnea, tachypnea, and tachycardia. Diagnosis is based on clinical presentation and chest x-ray. Treatment is with empirically chosen antibiotics. Prognosis is excellent for relatively young or healthy patients, but many pneumonias, especially when caused by *S. pneumoniae* or influenza virus, are fatal in older, sicker patients.

Etiology

Many organisms cause community-acquired pneumonia, including bacteria, viruses, and fungi. Pathogens vary by patient age and other factors (see Tables 196-1 and 196-2), but the relative importance of each as a cause of community-acquired pneumonia is uncertain, because most patients do not undergo thorough testing, and because even with testing, specific agents are identified in < 50% of cases.

S. pneumoniae, *H. influenzae*, *C. pneumoniae*, and *M. pneumoniae* are the most common bacterial causes. Pneumonia caused by chlamydia and mycoplasma are often clinically indistinguishable from other pneumonias. Common viral agents include respiratory syncytial virus (RSV), adenovirus, influenza viruses, metapneumovirus, and parainfluenza viruses. Bacterial superinfection can make distinguishing viral from bacterial infection difficult.

C. pneumoniae accounts for 2 to 5% of community-acquired pneumonia and is the 2nd most common cause of lung infections in healthy people aged 5 to 35 yr. *C. pneumoniae* is commonly responsible for outbreaks of respiratory infection within families, in college dormitories, and in military training camps. It causes a relatively benign form of pneumonia that infrequently requires hospitalization. *Chlamydia psittaci* pneumonia (psittacosis) is rare and occurs in patients who own or are often exposed to birds.

A host of other organisms causes lung infection in immunocompetent patients, although the term community-acquired pneumonia is usually reserved for the more common bacterial and viral etiologies.

Q fever, tularemia, anthrax, and plague are uncommon bacterial syndromes in which pneumonia may be a prominent feature; the latter three should raise the suspicion of bioterrorism.

Adenovirus, Epstein-Barr virus, and coxsackievirus are common viruses that rarely cause pneumonia. Varicella virus and hantavirus cause lung infection as part of adult chickenpox and hantavirus pulmonary syndrome; a coronavirus causes severe acute respiratory syndrome (SARS—see p. 1411).

Common fungal pathogens include *Histoplasma capsulatum* (histoplasmosis) and *Coccidioides immitis* (coccidioidomycosis). Less

[**Table 196-1.** Community-Acquired Pneumonia in Children]

common fungi include *Blastomyces dermatitidis* (blastomycosis) and *Paracoccidioides braziliensis* (paracoccidioidomycosis). *Pneumocystis jirovecii* commonly causes pneumonia in patients who have HIV infection or are immunosuppressed.

Parasites causing lung infection in developed countries include *Toxocara canis* or *T. catis* (visceral larva migrans), *Dirofilaria immitis* (dirofilariasis), and *Paragonimus westermani* (paragonimiasis). (For a discussion of pulmonary TB or of specific microorganisms, see p. 1302.)

Symptoms and Signs

Symptoms include malaise, cough, dyspnea, and chest pain. Cough typically is productive in older children and adults and dry in infants, young children, and the elderly. Dyspnea usually is mild and exertional and is rarely present at rest. Chest pain is pleuritic and is adjacent to the infected area. Pneumonia may manifest as upper abdominal pain when lower lobe infection irritates the diaphragm. Symptoms become variable at the extremes of age. Infection in infants may manifest as nonspecific irritability and restlessness; in the elderly, as confusion and obtundation.

Signs include fever, tachypnea, tachycardia, crackles, bronchial breath sounds, egophony, and dullness to percussion. Signs of pleural effusion may also be present (see p. 1998). Nasal flaring, use of accessory muscles, and cyanosis are common among infants. Fever is frequently absent in the elderly.

Symptoms and signs were previously thought to differ by type of pathogen, but presentations overlap considerably. In addition, no single symptom or sign is sensitive or specific enough to predict the organism. Symptoms are even similar for noninfective lung diseases such as pulmonary embolism, pulmonary cancer, and other inflammatory lung diseases.

Diagnosis

• Chest x-ray

• Consideration of pulmonary embolism

• Sometimes identification of pathogen

Diagnosis is suspected on the basis of clinical presentation and is confirmed by chest x-ray (see Table 196-3). The most serious condition misdiagnosed as pneumonia is pulmonary embolism, which may be more likely in patients with minimal sputum production, no accompanying URI or systemic symptoms, and risk factors for thromboembolism (see Table 194-1 on p. 1908).

Chest x-ray almost always shows some degree of infiltrate; rarely, an infiltrate is absent in the first 24 to 48 h of illness. In general, no specific findings distinguish one type of infection from another, although multilobar infiltrates suggest *S. pneumoniae* or *Legionella pneumophila* infection and interstitial pneumonia suggests viral or mycoplasmal etiology.

Hospitalized patients (see p. 1929) should undergo WBC count and electrolytes, BUN, and creatinine testing to classify risk and hydration status. Two sets of blood cultures are often obtained to detect pneumococcal bacteremia and sepsis, because about 12% of all patients hospitalized with pneumonia have bacteremia; *S. pneumoniae* accounts for two thirds of these cases. Whether the results of blood cultures alter therapy commonly enough to warrant the expense is under study. Pulse oximetry or ABG should also be done.

Pathogens: Attempts to identify a pathogen are not routinely indicated; exceptions may be made for critically ill patients, patients in whom a drug-resistant or unusual organism is suspected (eg, TB, *P. jirovecii*), and patients who are deteriorating or not responding to treatment within 72 h.

The use of Gram stain and culture of sputum for diagnosis is of uncertain benefit, because specimens often are contaminated and because overall diagnostic yield is low. Samples can be obtained noninvasively by simple expectoration or after hypertonic saline nebulization for those unable to produce sputum. Alternatively, patients can undergo bronchoscopy or endotracheal suctioning, either of which can be easily done through an endotracheal tube in mechanically ventilated patients. Testing should include mycobacterial and fungal stains and cultures in patients whose condition is deteriorating and in those unresponsive to broad-spectrum antibiotics.

Additional tests are indicated in some circumstances. Patients at risk of *Legionella* pneumonia (eg, patients who smoke, have chronic pulmonary disease, are > 40, receive chemotherapy

[**Table 196-2.** Community-Acquired Pneumonia in Adults*]

therapy, or take immunosuppressants for organ transplantation) should undergo testing for urinary *Legionella* antigen, which remains present long after treatment is initiated, but the test detects only *L. pneumophila* serogroup 1 (70% of cases). A 4-fold rise in antibody titers to ≥ 1:128 (or a single titer of ≥ 1:256 in a convalescent patient) is also considered diagnostic. These tests are specific (95 to 100%) but are not very sensitive (40 to 60%); thus, a positive test indicates infection, but a negative test does not

exclude it.

Infants and young children with possible RSV infection should undergo rapid antigen testing of specimens obtained with nasal or throat swabs. No other tests for viral pneumonias are done; viral culture and serologic tests are rarely clinically warranted.

PCR testing for mycoplasma and chlamydia species, although not widely available, holds promise as a highly sensitive and specific rapid diagnostic test and is likely to play a greater role as PCR technologies are refined.

Prognosis

Candidates for outpatient treatment usually improve over 24 to 72 h. Hospitalized patients

[**Table 196-3.** Probability of Pneumonia Given Chest X-Ray Infiltrate]

may improve or deteriorate depending on comorbidities. Aspiration is a major risk factor for death, as are older age and number and type of comorbidities. Pneumonia caused by certain organisms may also increase the risk of death. Death may be caused by pneumonia itself, progression to sepsis syndrome affecting other organs, or exacerbation of comorbidities.

Pneumococcal infection accounts for about two thirds of fatal cases of community-acquired pneumonia in which an etiologic agent is known. The overall mortality rate in hospitalized patients is about 12%. Poor prognostic factors include age < 1 or > 60 yr; involvement of > 1 lobe; peripheral WBC count < 5000/µL; comorbidities (eg, heart failure, alcoholism, hepatic or renal insufficiency), immunosuppression (eg, agammaglobulinemia, anatomic or functional asplenia), infection with serotypes 3 and 8; and hematogenous spread with either positive blood cultures or extrapulmonary complications (usually arthritis, meningitis, endocarditis). Infants and children are at special risk of pneumococcal otitis media, bacteremia, and meningitis.

Mortality in ***Legionella*** infection is 10 to 20% among community-acquired cases and is higher among immunosuppressed or hospitalized patients. Patients who respond do so slowly, and x-ray abnormalities usually persist for ≥ 1 mo. Most patients require hospitalization, many require ventilator support, and 10 to 20% die despite appropriate antibiotic therapy.

Prognosis in **mycoplasma** pneumonia is excellent; nearly all patients recover.

Chlamydophila pneumoniae responds more slowly to treatment than mycoplasma pneumonia and tends to recur if therapy is stopped prematurely. Young adults with *C. pneumoniae* usually do well, but the elderly have a mortality rate of 5 to 10%.

Treatment

• Risk stratification

• Antibiotics

• Antivirals for influenza or varicella

• Supportive measures

A prediction rule may be used to estimate mortality risk. The rule has been used to identify those patients who can be safely treated as outpatients and those who require hospitalization because of high risk of complications (see Table 196-4). However, the rule was not developed to determine site of care. Thus, the rule should supplement, not replace, clinical judgment, because many unrepresented factors, such as likelihood of adherence, ability to care for self, and wishes to avoid hospitalization, should also influence triage decisions. Also, certain criteria that extend across a conotinuum of severity have dichotomous cutoffs; eg, a heart rate of 124 beats/min may indicate distress, but points are not assigned unless heart

rate is ≥ 125 beats/min. ICU admission is required for patients who need mechanical ventilation and for those with hypotension (systolic BP < 90 mm Hg) that is unresponsive to volume resuscitation. Other criteria that mandate consideration for ICU admission include respiratory rate > 30/min, PaO_2/fraction of inspired O_2 (FIO_2) < 250, multilobar pneumonia, diastolic BP < 60 mm Hg, confusion, and BUN > 19.6 mg/dL.

Appropriate treatment involves starting antibiotics as soon as possible, preferably ≤ 8 h after presentation. Supportive care includes fluids, antipyretics, analgesics, and, for patients with hypoxemia, O_2.

Because organisms are difficult to identify, antibiotics are selected based on likely pathogens and severity of illness. Consensus guidelines have been developed by many professional organizations; one widely used set is detailed in Table 196-2. Guidelines should be adapted to local susceptibility patterns, drug formularies, and individual patient circumstances. Importantly, none provide recommendations for treatment of viral pneumonia.

Ribavirin and RSV Ig have been used alone and in combination for RSV bronchiolitis in children, but their effectiveness is controversial, and neither is standard practice. Ribavirin is not used in adults with RSV infection.

[**Table 196-4.** Risk Stratification for Community-Acquired Pneumonia]

Oseltamivir 75 mg po bid or zanamivir 10 mg inhaled bid started within 48 h of symptom onset and given for 5 days reduces the duration and severity of symptoms in patients who develop influenza infection. Acyclovir 5 to 10 mg/kg IV q 8 h for adults or 250 to 500 mg/m^2 body surface area IV q 8 h for children is recommended for varicella lung infections. Some patients with viral pneumonia, especially those with influenza, develop superimposed bacterial infections and require antibiotics directed against *S. pneumoniae*, *H. influenzae*, and *Staphylococcus aureus*.

With empiric treatment, 90% of patients with bacterial pneumonia improve. Improvement is manifested by decreased cough and dyspnea, defervescence, relief of chest pain, and decline in WBC count. Failure to improve should trigger suspicion of an unusual organism, resistance to the antimicrobial used for treatment, empyema, coinfection or superinfection with a 2nd infectious agent, an obstructive endobronchial lesion, immunosuppression, metastatic focus of infection with reseeding (in the case of pneumococcal infection), or nonadherence to treatment (in the case of outpatients). If none of these can be proved, treatment failure is likely due to inadequate host defenses.

Most viral pneumonias resolve without specific treatment.

Chest physical therapy can be used to treat pneumonia; however, there is no clear evidence for its efficacy. Follow-up x-rays should be obtained 6 wk after treatment in patients > 35; persistence of an infiltrate at ≥ 6 wk raises suspicions of an underlying, possibly malignant endobronchial lesion or of TB.

Prevention

Some forms of community-acquired pneumonia are preventable with pneumococcal conjugate vaccine (for patients < 2 yr), *H. influenzae* type b (Hib) vaccine (for patients < 2 yr), pneumococcal pneumonia vaccine (for patients at high risk, such as those with underlying heart, lung, or immune system disorders), varicella vaccine (for patients < 18 mo and a later booster vaccine), and influenza vaccine (for patients age ≥ 65 and those at high risk—see Table 131-2 on p. 1174 and see Table 268-10 on p. 2718). Oseltamivir 75 mg po once/day or zanamivir 10 mg once/day can be given for 2 wk to prevent influenza (although resistance has recently been described for oseltamivir) for household contacts of patients with influenza and to high-risk patients not vaccinated against influenza during influenza epidemics. Pneumococcal pneumonia vaccination is recommended for all patients ≥ 65 (see p. 1177).

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia (HAP) develops at least 48 h after hospital admission. The most common pathogens are gram-negative bacilli and *Staphylococcus aureus*; drug-resistant organisms are an important concern. Symptoms and signs are the same as those for community-acquired pneumonia, but in ventilated patients, pneumonia may also manifest as worsening oxygenation and increased tracheal secretions. Diagnosis is suspected on the basis of clinical presentation and chest x-ray and is confirmed by blood culture or bronchoscopic sampling of the lower respiratory tract. Treatment is with antibiotics. Overall prognosis is poor, due in part to comorbidities.

HAP includes ventilator-associated pneumonia (VAP), postoperative pneumonia, and pneumonia that develops in unventilated but otherwise moderately or critically ill hospitalized inpatients. It also includes the new category healthcare-associated pneumonia (HCAP), which refers to pneumonia acquired by patients in healthcare facilities such as chronic care facilities, dialysis centers, and infusion centers.

Etiology

The most common cause is microaspiration of bacteria that colonize the oropharynx and upper airways in seriously ill patients.

Risk factors: Endotracheal intubation with mechanical ventilation poses the greatest overall risk; VAP constitutes > 85% of all cases, with pneumonia occurring in 17 to 23% of ventilated patients. Endotracheal intubation breaches airway defenses, impairs cough and mucociliary clearance, and facilitates microaspiration of bacteria-laden secretions that pool above the inflated endotracheal tube cuff. In addition, bacteria form a biofilm on and within the endotracheal tube that protects them from antibiotics and host defenses.

In nonintubated patients, risk factors include previous antibiotic treatment, high gastric pH (due to stress ulcer prophylaxis or therapy), and coexisting cardiac, pulmonary, hepatic, or renal insufficiency. Major risk factors for postoperative pneumonia are age > 70, abdominal or thoracic surgery, and dependent functional status.

Pathogens: Pathogens and antibiotic resistance patterns vary significantly among institutions and can vary within institutions over short periods (eg, month to month). In general, the most important pathogen is *Pseudomonas aeruginosa*, which is especially common in pneumonias acquired in intensive care settings and in patients with cystic fibrosis, neutropenia, advanced AIDS, and bronchiectasis. Other important pathogens include enteric gram-negative bacteria (mainly *Enterobacter* sp, *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Proteus* sp, and *Acinetobacter* sp) and both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*.

S. aureus, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are most commonly implicated when pneumonia develops within 4 to 7 days of hospitalization, whereas enteric gram-negative organisms become more common with increasing duration of intubation. Patients with HAP due to *S. aureus* or gram-negative bacilli tend to be elderly or have serious circumstances, such as needing a ventilator, undergoing chemotherapy for cancer, or having chronic pulmonary disease.

Prior antibiotic treatment greatly increases the likelihood of polymicrobial infection, resistant organisms, particularly methicillin-resistant *S. aureus*, and *Pseudomonas* infection. Infection with a resistant organism markedly worsens mortality and morbidity.

High-dose corticosteroids increase the risk of *Legionella* and *Pseudomonas* infections.

Symptoms and Signs

Symptoms and signs in nonintubated patients are generally the same as those for community-acquired pneumonia (see p. 1925). Pneumonia in critically ill, mechanically ventilated patients more typically causes fever and increased respiratory rate or heart rate or changes in respiratory parameters, such as an increase in purulent secretions or worsening hypoxemia.

Diagnosis

• Chest x-ray and clinical criteria (limited accuracy)

• Sometimes bronchoscopy, blood cultures

Diagnosis is imperfect. In practice, HAP is often suspected on the basis of the appearance of a new infiltrate on a chest x-ray that is taken for evaluation of new symptoms or signs or of leukocytosis. However, no symptom, sign, or x-ray finding is sensitive or specific for the diagnosis, because all can be caused by atelectasis, pulmonary embolism, or pulmonary edema and may be part of the clinical findings in acute respiratory distress syndrome. Alternative diagnoses should be sought, particularly in patients who have a pneumonia risk score < 6 (see Table 196-5).

Gram stain and culture of endotracheal aspirates are of uncertain benefit, because specimens are likely to be contaminated with bacteria that are colonizers as well as pathogens, and a positive culture may or may not

[**Table 196-5.** Hospital-Acquired Pneumonia Risk Index]

indicate infection. Bronchoscopic sampling of lower airway secretions for quantitative culture seems to yield more reliable specimens, but the effect of this approach on outcomes is undetermined. Measurement of inflammatory mediators in bronchoalveolar lavage fluid may play a future role in diagnosis; eg, a concentration of soluble triggering receptor expressed on myeloid cells (a protein expressed and shed by immune cells during infection) > 5 pg/mL may help distinguish bacterial and fungal pneumonia from noninfectious causes of clinical and radiographic changes in ventilated patients. However, this approach requires further investigation. The only finding that reliably identifies both pneumonia and the responsible organism is a pleural fluid culture that is positive for a respiratory pathogen. Blood cultures are relatively specific if a respiratory pathogen is identified but are insensitive.

Prognosis

The mortality associated with HAP due to gram-negative infection is about 25 to 50% despite the availability of effective antibiotics. Whether death is due to underlying illness or to the pneumonia itself is uncertain. Women may be at greater risk of death. The mortality rate with *S. aureus* pneumonia is 10 to 40%, in part due to the serious circumstances with which it is associated.

Treatment

• Empirically chosen antibiotics active against resistant gram-negative and gram-positive organisms

If the diagnosis is suspected, treatment is with antibiotics that are chosen empirically based on local sensitivity patterns, specific patient risk factors, and the conditions noted in Table 196-2.

Indiscriminate use of antibiotics is a major contributor to development of antimicrobial resistance. Therefore, treatment may begin with initial use of broad-spectrum drugs, which are replaced by the most specific drug available for the pathogens identified by culture. Alternative strategies for limiting resistance that have not proved effective include stopping antibiotics after 72 h in patients whose pulmonary infection scores (see Table 196-5) improve to < 6 and regularly rotating empirically chosen antibiotics (eg, q 3 to 6 mo).

Multiple regimens exist, but all should include antibiotics that are effective against both resistant gram-negative and gram-positive organisms. Options include

• A carbapenem (imipenem/cilastatin 500 mg IV q 6 h or 1 g q 8 h or meropenem 1 g IV q 8 h), monobactam (aztreonam 1 to 2 g IV q 8 h), or piperacillin/tazobactam 4.5 g q 6 h

• Ceftazidime 2 g IV q 8 h or cefepime 1 to 2 g q 8 to 12 h

• These drugs are given alone or combined with vancomycin 15 mg/kg q 12 h

Linezolid 600 mg IV q 12 h may be used for some pulmonary infections involving methicillin-resistant *S. aureus*. Daptomycin should not be used for pulmonary infections.

Prevention

Most measures focus on preventing VAP. Semiupright or upright positioning reduces risk of aspiration and pneumonia compared with recumbent positioning and is the simplest and most effective preventive method. Noninvasive ventilation using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) prevents the breach in airway defense that occurs with endotracheal intubation and eliminates the need for intubation in some patients.

Continuous aspiration of subglottic secretions using a specially designed endotracheal tube attached to a suction device seems to reduce the risk of aspiration.

Selective decontamination of the oropharynx (using topical gentamicin, colistin, chlorhexidine, vancomycin cream, or a combination) or of the entire GI tract (using polymyxin, an aminoglycoside or quinolone, and either nystatin or amphotericin B) is controversial because of concerns about resistant strains and because decontamination, although it decreases incidence of HAP, has not been shown to decrease mortality.

Surveillance cultures and routinely changing ventilator circuits or endotracheal tubes have not been shown to decrease VAP.

Incentive spirometry is recommended to help prevent postoperative pneumonia.

Nursing Home-Acquired Pneumonia

Common nursing home-acquired pneumonia pathogens include gram-negative bacilli, *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, anaerobes, and influenza viruses. Symptoms and signs are similar to those of pneumonia that occurs in other settings, except many elderly patients have less prominent changes in vital signs. Diagnosis is based on clinical presentation and chest x-ray, which is often not immediately available in nursing homes. Treatment is with antibiotics provided in the nursing home for less severe illness and in the hospital for more severe illness. Mortality is moderately high but may be due in part to comorbidities.

Nursing home-acquired pneumonia falls between community-acquired and hospital-acquired pneumonia in etiology and management. *Streptococcus pneumoniae* and gram-negative bacilli may be roughly equally responsible for most infections, though there is debate over whether gram-negative bacilli are pathogens or merely colonizers. *Haemophilus influenzae* and *Moraxella catarrhalis* are next most common; *Chlamydia*, *Mycoplasma*, and *Legionella* spp are rarely identified. Risk factors are common among debilitated nursing home residents; they include poor functional status, mood disorder, altered mental status, difficulty swallowing, immunosuppression, older age, use of tube feedings, influenza or other viral respiratory infections, conditions that predispose to bacteremia (eg, indwelling bladder catheter, pressure ulcers), and presence of a tracheostomy tube.

Symptoms and Signs

Symptoms often resemble those of community-acquired or hospital-acquired pneumonia but may be more subtle. Cough and altered mental status are common, as are nonspecific symptoms of anorexia, weakness, restlessness and agitation, falling, and incontinence. Subjective dyspnea occurs but is less common. Signs include diminished or absent responsiveness, fever, tachycardia, tachypnea, wheezes or crackles, and stertorous, wet breathing.

Diagnosis

• Clinical manifestations

• Chest x-ray

• Assessment of renal function and oxygenation

Diagnosis is based on clinical manifestations and chest x-ray. Because detection of physical changes may be delayed in a nursing home setting and because these patients are at greater risk of complications, evaluation for hypoxemia with pulse oximetry and for decreased intravascular volume with serum BUN and creatinine should also be done.

X-rays are often difficult to obtain in nursing home patients, so it may be necessary to transfer them to a hospital at least for initial evaluation. In some cases (eg, if clinical diagnosis is clear, if illness is mild, or if aggressive care is not the goal), treatment may be started without x-ray confirmation. It is thought that nursing home patients may initially lack a radiographic infiltrate, presumably because of the dehydration that commonly accompanies febrile pneumonia in the elderly or a blunted immune response, although the phenomenon is not proved to occur.

Prognosis

Mortality rate for patients requiring admission for treatment is 13 to 41%, whereas that for patients treated in the nursing home is 7 to 19%. Mortality rate exceeds 30% in patients with > 2 of the following findings:

• Respiratory rate > 30 breaths/min

• Heart rate > 125 beats/min

• Acute mental status change

• History of dementia

An alternative predictive index incorporates laboratory data (see Table 196-6). Physicians should follow all medical directives, because pneumonia is often a terminal event in debilitated nursing home patients.

Treatment

• Antibiotics given before hospitalization in patients being hospitalized

Few data are available to guide decisions about where treatment should take place. In general, patients should be hospitalized if they have ≥ 2 unstable vital signs and if the nursing home cannot administer acute care. Some nursing home patients are not candidates for aggressive treatment or hospital transfer under any circumstances. In patients who are to be hospitalized, one dose of antibiotics that are effective against *S. pneumoniae*, *H. influenzae*, and common gram-negative bacilli should be given before transfer; a common regimen is an oral antipneumococcal quinolone (eg, levofloxacin 750 mg once/day or moxifloxacin 400 mg once/day). Ceftriaxone, ertapenem, and ampicillin/sulbactam (each as monotherapy) are alternatives.

Pneumonia in Immunocompromised Patients

Pneumonia in immunocompromised patients is often caused by unusual pathogens. Symptoms and signs depend on the pathogen. Diagnosis is based on blood cultures and bronchoscopic sampling of respiratory secretions, sometimes with quantitative cultures. Treatment depends on the host defect and pathogen.

The potential pathogens in patients with compromised defenses are legion. Likely pathogens based on

the type of defect in host defenses are listed in Table 196-7. However, respiratory symptoms and changes on chest x-rays in immunocompromised patients may be due to various processes other than infection, such as pulmonary hemorrhage, pulmonary edema, radiation injury, pulmonary toxicity due to cytotoxic drugs, and tumor infiltrates.

[**Table 196-6.** Nursing Home-Acquired Pneumonia Risk Index]

[**Table 196-7.** Pneumonia in Immunocompromised Patients]

Symptoms and Signs

Symptoms and signs may be the same as those found with community-acquired or hospital-acquired pneumonia in immunocompetent patients, though immunocompromised patients may have no fever or respiratory signs and are less likely to have purulent sputum if they are neutropenic. In some patients, the only sign is fever.

Diagnosis

• Chest x-ray

• Assessment of oxygenation

• Induction or bronchoscopy to obtain sputum

• Blood cultures

• Pathogens predicted based on symptoms, x-ray changes, and type of immunodeficiency

An immunocompromised patient with respiratory symptoms, signs, or fever should undergo chest x-ray and assessment of oxygenation (usually by pulse oximetry). If an infiltrate is present, diagnostic studies should include sputum Gram stain and culture and blood cultures. Chest x-ray may be normal in *Pneumocystis jirovecii* pneumonia, but hypoxia is usually present. Optimally, a firm diagnosis is made with induced sputum, bronchoscopy, or both, especially in patients with chronic pneumonia, atypical presentation, severe defects in immune function, or failure to respond to broad-spectrum antibiotics.

Likely pathogens can often be predicted based on symptoms, x-ray changes, and the type of immunodeficiency. In patients with acute symptoms, likely diagnoses are bacterial infection, hemorrhage, pulmonary edema, a leukocyte agglutinin reaction, and pulmonary emboli. A subacute or chronic presentation is more suggestive of a fungal or mycobacterial infection, an opportunistic viral infection, *P. jirovecii* pneumonia, tumor, a cytotoxic drug reaction, or radiation injury.

X-rays showing localized consolidation usually indicate an infection involving bacteria, mycobacteria, fungi, or *Nocardia* sp. A diffuse interstitial pattern is more likely to represent a viral infection, *P. jirovecii* pneumonia, drug or radiation injury, or pulmonary edema. Diffuse nodular lesions suggest mycobacteria, *Nocardia* sp, fungi, or tumor. Cavitary disease suggests mycobacteria, *Nocardia* sp, fungi, or bacteria.

In organ or marrow transplantation recipients with bilateral interstitial pneumonia, the usual cause is cytomegalovirus, or the disease is idiopathic. A pleural-based consolidation is usually aspergillosis. In AIDS patients, bilateral pneumonia is usually *P. jirovecii* pneumonia. About 30% of patients with HIV infection have *P. jirovecii* pneumonia as the initial AIDS-defining diagnosis, and > 80% of AIDS patients have this infection at some time if prophylaxis is not given (see p. 1455). Patients with HIV infection become vulnerable to *P. jirovecii* pneumonia when the $CD4^+$ helper cell count is < 200/μL.

Treatment

• Broad-spectrum antimicrobial therapy

In neutropenic patients, empiric treatment depends on the host defect, x-ray, and severity of illness. Generally, broad-spectrum drugs are needed to cover gram-negative bacilli, *Staphylococcus aureus*, and anaerobes, as for hospital-acquired pneumonia (see p. 1931). If patients with conditions other than HIV do not improve with 5 days of antibiotic therapy, antifungal therapy is frequently added empirically.

Pneumocystis jirovecii Pneumonia

***P. jirovecii* is a common cause of pneumonia in immunosuppressed patients, especially in those infected with HIV and in those receiving systemic corticosteroids. Symptoms include fever, dyspnea, and dry cough. Diagnosis requires demonstration of the organism in an induced sputum specimen or bronchoscopic brushing. Treatment is with antibiotics, usually trimethoprim/sulfamethoxazole or dapsone/trimethoprim, clindamycin/primaquine, atovaquone, or pentamidine. Patients with PaO_2 < 70 mm Hg receive systemic corticosteroids. Prognosis is generally good with timely treatment.**

P. jirovecii is a ubiquitous organism transmitted by aerosol route and causes no disease in immunocompetent patients. Patients with HIV infection and CD4+ counts < 200/µL, organ transplant recipients, patients who have hematologic cancers, and patients taking corticosteroids are at risk of developing *P. jirovecii* pneumonia. Most have fever, dyspnea, and a dry, nonproductive cough that evolves subacutely over several weeks (HIV infection) or acutely over several days (other causes of compromised cell-mediated immunity).

Diagnosis

• Chest x-ray

• Pulse oximetry

• Histopathologic confirmation

Patients should have chest x-ray and assessment of oxygenation by pulse oximetry. The chest x-ray characteristically shows diffuse, bilateral perihilar infiltrates, but 20 to 30% of patients have normal x-rays. However, hypoxemia is often present even when chest x-ray shows no infiltrate; this finding can be an important clue to diagnosis. When pulse oximetry is abnormal, ABGs are often obtained to show severity of hypoxemia (including an increase in the alveolar-arterial O_2 gradient). If obtained, pulmonary function tests show altered diffusing capacity (although this is rarely done as a diagnostic test).

Confirmation of diagnosis requires histopathologic demonstration of the organism with methenamine silver, Giemsa, Wright-Giemsa, modified Grocott, Weigert-Gram, or monoclonal antibody stain. Sputum specimens are usually obtained by induced sputum or bronchoscopy. Sensitivity ranges from 30 to 80% for induced sputum and is > 95% for bronchoscopy with bronchoalveolar lavage.

Prognosis

Overall mortality for *P. jirovecii* pneumonia in hospitalized patients is 15 to 20%. Risk factors for death may include previous history of *P. jirovecii* pneumonia, older age, and, in HIV-infected patients, CD4+ cell count < 50/µL.

Treatment

• Trimethoprim/sulfamethoxazole

• Corticosteroids if PaO_2 < 70 mm Hg

Treatment is with trimethoprim/sulfamethoxazole (TMP/SMX) 4 to 5 mg/kg IV or po tid for 14 to 21 days. Treatment can be started before diagnosis is confirmed because *P. jirovecii* cysts persist in the lungs for weeks. Adverse effects of treatment are more common among patients with AIDS and include rash,

neutropenia, hepatitis, and fever. Alternative regimens are pentamidine 4 mg/kg IV once/day; atovaquone 750 mg po bid; TMP 5 mg/kg po qid with dapsone 100 mg po once/day; or clindamycin 300 to 900 mg IV q 6 to 8 h with primaquine base 15 to 30 mg/day po, also for 21 days. The major limitation of pentamidine is the high frequency of toxic adverse effects, including renal failure, hypotension, and hypoglycemia. Adjunctive therapy with corticosteroids is recommended for patients with a PaO_2 < 70 mm Hg. The suggested regimen is prednisone 40 mg bid (or its equivalent) for the first 5 days, 40 mg once/day for the next 5 days (or 20 mg bid), and then 20 mg once/day for the duration of treatment.

Prevention

HIV-infected patients who have had *P. jirovecii* pneumonia or who have a CD4+ count < 200/µL should receive prophylaxis with TMP/SMX 80/400 mg once/day; if this regimen is not tolerated, dapsone 100 mg po once/day or aerosolized pentamidine 300 mg once/month can be used. These prophylactic regimens are also probably indicated for non-HIV-infected patients at risk of *P. jirovecii* pneumonia.

Aspiration Pneumonitis and Pneumonia

Aspiration pneumonitis and pneumonia are caused by inhaling toxic substances, usually gastric contents, into the lungs. Chemical pneumonitis, bacterial pneumonia, or airway obstruction can occur. Symptoms include cough and dyspnea. Diagnosis is based on clinical presentation and chest x-ray findings. Treatment and prognosis differ by aspirated substance.

Aspiration can cause lung inflammation (chemical pneumonitis), infection (bacterial pneumonia or abscess), or airway obstruction. However, most episodes of aspiration cause minor symptoms or pneumonitis rather than infection or obstruction, and some patients aspirate with no sequelae. Drowning is discussed on p. 3279; airway obstruction is discussed on p. 2269.

Risk factors for aspiration include impaired cognition, impaired swallowing, vomiting, GI and respiratory devices and procedures (eg, nasogastric or endotracheal tube placement, dental work), and gastroesophageal reflux disease.

Pathophysiology

Chemical pneumonitis: Multiple substances are directly toxic to the lungs or stimulate an inflammatory response when aspirated; gastric acid is the most common such aspirated substance, but others include petroleum products (particularly of low viscosity, such as petroleum jelly) and laxative oils (such as mineral, castor, and paraffin oil), all of which cause lipoid pneumonia. Aspirated gasoline and kerosene also cause a chemical pneumonitis (see p. 3339).

Gastric contents cause damage mainly from gastric acid, although food and other ingested material (eg, activated charcoal as in treatment of overdose) are injurious in quantity. Gastric acid causes a chemical burn of the airways and lung leading to rapid bronchoconstriction, atelectasis, edema, and alveolar hemorrhage. Symptoms include acute dyspnea with cough that is sometimes productive of pink frothy sputum, tachypnea, tachycardia, fever, diffuse crackles, and wheezing. Chest x-ray shows diffuse infiltrates frequently but not exclusively in dependent segments, while pulse-oximetry and ABGs demonstrate hypoxemia. Treatment is supportive, often involving supplemental O_2 and mechanical ventilation. Antibiotics often are given to patients with witnessed or known gastric aspiration. The syndrome may resolve spontaneously, usually within a few days, or may progress to acute respiratory distress syndrome. Sometimes bacterial superinfection occurs.

Oil or petroleum jelly aspiration causes exogenous lipoid pneumonia, which is characterized histologically by chronic granulomatous inflammation with fibrosis. It is often asymptomatic and is detected incidentally on chest x-ray or may manifest with low-grade fever, gradual weight loss, and crackles. Chest x-ray findings vary; consolidation, cavitation, interstitial or nodular infiltrates, pleural effusion, and other changes may be slowly progressive. Treatment is avoidance of the toxic substance. Anecdotal reports suggest systemic corticosteroids may be beneficial.

Aspiration pneumonia: Healthy people commonly aspirate small amounts of oral secretions, but normal

defense mechanisms usually clear the inoculum without sequelae. Aspiration of larger amounts, or aspiration in a patient with impaired pulmonary defenses, often causes pneumonia and/or abscess (see also Ch. 197). Elderly patients tend to aspirate because of conditions associated with aging that alter consciousness, such as sedative use and disorders (eg, neurologic disorders, weakness). Empyema (see p. 1998) also occasionally complicates aspiration.

Anaerobes often can be cultured from sputum, but it is unclear whether they are primary infecting organisms to which treatment should be directed or whether they are simply one of several organisms causing infection.

Symptoms and Signs

Symptoms and signs of pneumonia and abscess are similar and include chronic low-grade dyspnea, fever, weight loss, and cough productive of putrid, foul-tasting sputum. Patients may have signs of poor oral hygiene.

Diagnosis

• Chest x-ray

Chest x-ray shows an infiltrate, frequently but not exclusively, in the dependent lung segments, ie, the superior or posterior basal segments of a lower lobe or the posterior segment of an upper lobe.

Treatment

• Antibiotics, usually clindamycin

Abscess: Treatment of lung abscess is with clindamycin 450 to 900 mg IV q 8 h followed by 300 mg po qid once fever and clinical symptoms subside. An alternative is a combination of penicillin (either penicillin G 1 to 2 million units q 4 to 6 h or amoxicillin 0.5 to 1 g po tid) plus either metronidazole 500 mg po tid, amoxicillin/clavulanate 875/125 mg po tid, or imipenem. Treatment is continued for 6 wk to 3 mo.

Pneumonia: Treatment of aspiration pneumonia can be with clindamycin, but other antibiotics with lower risk of adverse effects may be effective, because it is not clear that all the anaerobes cultured from the infection require specific treatment. Duration of treatment is usually 1 to 2 wk.

Chapter 197. Lung Abscess

Introduction

Lung abscess is a necrotizing lung infection characterized by a pus-filled cavitary lesion. It is almost always caused by aspiration of oral secretions by patients who have impaired consciousness. Symptoms are persistent cough, fever, sweats, and weight loss. Diagnosis is based primarily on chest x-ray. Treatment usually is with clindamycin or combination β-lactam/β-lactamase inhibitors.

Etiology

Most lung abscesses develop after aspiration of oral secretions by patients with gingivitis or poor oral hygiene. Typically, patients have altered consciousness as a result of alcohol intoxication, illicit drugs, anesthesia, sedatives, or opioids. Older patients and those unable to handle their oral secretions, often because of neurologic disease, are also at risk.

A less common cause of lung abscess is necrotizing pneumonia that may develop from hematogenous seeding of the lungs due to suppurative thromboembolism (eg, septic embolism due to IV drug use) or right-sided endocarditis. In contrast to aspiration, these conditions typically cause multiple rather than isolated lung abscesses.

The most common pathogens of lung abscesses due to aspiration are anaerobic bacteria, but about half of all cases involve both anaerobic and aerobic organisms (see Table 197-1). The most common aerobic pathogens are streptococci and staphylococci—sometimes methicillin-resistant *Staphylococcus aureus* (MRSA). An unusual but very important acute and often lethal form of lung necrosis is caused by *S. aureus* with genes for Panton-Valentine leukocidin. Very serious and fulminant cases may be caused by MRSA (USA 300 strain), which has become a rare but very important cause of necrotizing pneumonia in young previously healthy adults and children. Occasionally, cases are due to gram-negative bacteria, especially *Klebsiella*. Immunocompromised patients with lung abscess may have infection with *Nocardia*, *Mycobacteria* sp, or fungi. Some people, especially those from developing countries, are at risk of abscess due to *Mycobacterium tuberculosis*, and rare cases are due to amebic infection (eg, with *Entamoeba histolytica*), paragonimiasis, or *Burkholderia pseudomallei*.

Introduction of these pathogens into the lungs first causes inflammation, which leads to tissue necrosis and then abscess formation. The abscess usually ruptures into a bronchus, and its contents are expectorated, leaving an air- and fluid-filled cavity. In about one third of cases, direct or indirect extension (via bronchopleural fistula) into the pleural cavity results in empyema.

Cavitary pulmonary lesions are not always caused by infection. Noninfectious causes include the following:

- Bullae with air-fluid level
- Bronchiectasis
- Lung cancer
- Lung infarction
- Nodular silicosis nodule with central necrosis
- Pulmonary embolism
- Pulmonary sequestration
- Sarcoidosis

• Wegener's granulomatosis

Symptoms and Signs

Symptoms of abscess due to anaerobic bacteria or mixed anaerobic and aerobic bacteria

[Table 197-1. Infectious Causes of Cavitary Lung Lesions]

are usually chronic (eg, over weeks or months) and include productive cough, fever, sweats, and weight loss. Severe prostration may occur. Sputum may be purulent or blood-streaked and classically smells or tastes foul. Symptoms of abscess due to aerobic bacteria develop more acutely and resemble bacterial pneumonia. Abscesses due to organisms other than anaerobes (eg, *Mycobacteria*, *Nocardia*) lack putrid respiratory secretions and may be more likely to occur in nondependent lung regions.

Signs of lung abscess, when present, are nonspecific and resemble those of pneumonia: decreased breath sounds indicating consolidation or effusion, temperature ≥ 38°C, crackles over the affected area, egophony, and dullness to percussion in the presence of effusion. Patients typically have signs of periodontal disease and a history of a predisposing cause of aspiration, such as dysphagia or a condition causing impaired consciousness.

Diagnosis

• Chest x-ray

• CT as needed

• Sputum cultures (unless anaerobic infection is very likely), including for fungi and mycobacteria

• Bronchoscopy as needed to exclude cancer

Lung abscess is suspected based on history in a patient who is aspiration-prone due to altered consciousness or dysphagia and is confirmed by chest x-ray. In an anaerobic infection due to aspiration, chest x-ray classically shows consolidation with a single cavity containing an air-fluid level in portions of the lung that would be dependent when the patient is recumbent (eg, the posterior segments of the upper lobes or the superior or lateral basal segments of the lower lobes). This pattern helps distinguish anaerobic abscess from other causes of cavitary pulmonary disease, because diffuse or embolic pulmonary disease often causes multiple cavitations, and TB typically involves the apices.

CT is not routinely needed but may be useful when the x-ray suggests a cavitating lesion or when an underlying pulmonary mass obstructing the drainage of a lung segment is suspected.

Bronchial carcinoma can lead to obstruction that causes pneumonia and abscess formation. This should be suspected in smokers, recent smokers, and patients with unexplained cavitary lesions and no fever. Bronchoscopy is sometimes done to exclude cancer or the presence of a foreign body or to detect unusual pathogens, such as fungi.

Cultures: Anaerobic bacteria are rarely identifiable on culture because uncontaminated specimens are difficult to obtain and because most laboratories do not culture anaerobes well or often. If sputum is putrid, then anaerobic infection is assumed to be the cause. However, if empyema is present, pleural fluid provides a good source for anaerobic culture.

When clinical findings make anaerobic infection less likely, aerobic, fungal, or mycobacterial infection should be suspected, and attempts should be made to identify a pathogen. Cultures of sputum, bronchoscopic aspirates, or both are helpful. MRSA is generally found in both the sputum and blood cultures.

Treatment

• IV antibiotics or, for less seriously affected patients, oral antibiotics

• Percutaneous drainage or surgery if empyema present or no response to antibiotics

Treatment is with antibiotics. Clindamycin 600 mg IV q 6 to 8 h is usually the drug of choice because it has excellent activity against streptococci and anaerobic organisms. The primary alternative is a combination β-lactam/β-lactamase inhibitor (eg, ampicillin/sulbactam 1 to 2 g IV q 6 h, ticarcillin/clavulanate 3 to 6 g IV q 6 h, piperacillin/tazobactam 3 g IV q 6 h). Metronidazole 500 mg q 8 h may be used but must be combined with penicillin 2 million units q 6 h IV. Less seriously ill patients may be given oral antibiotics such as clindamycin 300 mg po q 6 h or amoxicillin/clavulanate 875/125 mg po q 12 h. IV regimens can be converted to oral ones when the patient defervesces. For very serious infections involving MSRA, the best treatment is vancomycin or linezolid.

Optimal duration of treatment is unknown, but common practice is to treat until the chest x-ray shows complete resolution, which generally takes 3 to 6 wk or longer. In general, the larger the abscess, the longer it will take for x-rays to show resolution.

Most authorities do not recommend chest physical therapy and postural drainage because they may cause spillage of infection into other bronchi with extension of the infection or acute obstruction. If the patient is weak or paralyzed or has respiratory failure, tracheostomy and suctioning may be necessary. Rarely, bronchoscopic aspiration helps facilitate drainage. An accompanying empyema must be drained. Percutaneous or surgical drainage of lung abscesses is necessary in the roughly 10% of patients in whom lesions do not respond to antibiotics. Resistance to antibiotic treatment is most common with large cavities and with infections that complicate obstructions.

When surgery is necessary, lobectomy is the most common procedure; segmental resection may suffice for small lesions (< 6 cm diameter cavity). Pneumonectomy may be necessary for multiple abscesses or for pulmonary gangrene unresponsive to drug therapy.

Chapter 198. Bronchiectasis

Introduction

Bronchiectasis is dilation and destruction of larger bronchi caused by chronic infection and inflammation. Common causes are cystic fibrosis, immune defects, and recurrent infections, though some cases seem to be idiopathic. Symptoms are chronic cough and purulent sputum expectoration; some patients may also have fever and dyspnea. Diagnosis is based on history and imaging, usually involving high-resolution CT, though standard chest x-rays may be diagnostic. Treatment and prevention of acute exacerbations are with antibiotics, drainage of secretions, and management of complications, such as superinfection and hemoptysis. Treatment of underlying disorders is important whenever possible.

Etiology

Bronchiectasis may affect many areas of the lung (diffuse bronchiectasis), or it may appear in only one or two areas (focal bronchiectasis). Diffuse bronchiectasis develops in patients with genetic, immune, or anatomic defects that affect the airways. Cystic fibrosis is the most common cause. Immunodeficiencies may also cause diffuse disease, as may rare abnormalities in airway structure. Diffuse bronchiectasis is an uncommon complication of more common conditions, such as RA or Sjogren's syndrome. Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to *Aspergillus* sp (see p. 1887). It occurs primarily in people with asthma and less commonly in people with cystic fibrosis and can lead to bronchiectasis.

Focal bronchiectasis develops from untreated pneumonia or obstruction (eg, due to foreign bodies and tumors). Mycobacteria can cause focal bronchiectasis as well as colonize the lungs of patients with bronchiectasis due to other disorders (see Table 198-1). Some cases have no readily apparent cause.

Pathophysiology

All the causative conditions impair airway clearance mechanisms and host defenses, resulting in an inability to clear secretions, which, in turn, predisposes patients to chronic infection and inflammation. As a result of frequent infections, most commonly with *Haemophilus influenzae* (35%), *Pseudomonas aeruginosa* (31%), *Moraxella catarrhalis* (20%), *Staphylococcus aureus* (14%), and *Streptococcus pneumoniae* (13%), airways become inspissated with viscous mucous containing inflammatory mediators and pathogens and slowly become dilated, scarred, and distorted. Histologically, bronchial walls are thickened by edema, inflammation, and neovascularization. Destruction of surrounding interstitium and alveoli causes fibrosis, emphysema, or both.

Superinfection with multidrug-resistant organisms, including *Mycobacterium tuberculosis*, and mycobacteria other than *M. tuberculosis* can cause recurrent exacerbations and worsen airflow limitation on pulmonary function tests. Pulmonary hypertension and right-sided heart failure may ensue because functional lung tissue decreases.

Symptoms and Signs

Symptoms characteristically begin insidiously and gradually worsen over years. The major presenting symptom of bronchiectasis

[**Table 198-1.** Factors Predisposing to Bronchiectasis]

is chronic cough that almost always produces large volumes of thick, tenacious, purulent sputum. Dyspnea and wheezing are common. Hemoptysis, which can be massive, is due to neovascularization of the airways from the bronchial (as opposed to pulmonary) arteries. Acute exacerbations of disease due to new or worsened infection increase the extent of cough and the volume and purulence of sputum production. Low-grade fever may also be present.

Halitosis and abnormal breath sounds, including crackles, rhonchi, and wheezing, are typical signs of disease. Finger clubbing may also be present. In advanced cases, hypoxemia and signs of pulmonary hypertension (eg, shortness of breath, dizziness) and right-sided heart failure can occur.

Diagnosis

• History and physical examination

• Chest x-ray

• High-resolution CT for confirmation

• Pulmonary function tests for baseline function and progression of disease

• Specific tests for suspected causes

Diagnosis is based on a history, physical examination, and radiologic testing, beginning with a chest x-ray. Chronic bronchitis may mimic bronchiectasis clinically, but bronchiectasis is distinguished by more voluminous daily production of purulent sputum and by dilated airways on imaging studies.

Imaging: X-ray findings suggestive of bronchiectasis include scattered irregular opacities caused by mucous plugs, honeycombing, and rings and "tram lines" caused by thickened, dilated airways located perpendicular to the x-ray beam. Radiographic patterns may differ by underlying disease: Bronchiectasis due to cystic fibrosis develops predominantly in upper lobes, whereas that due to other causes is more diffuse or predominates in the lower lobes.

High-resolution CT is the test of choice for defining the extent of bronchiectasis. The test is nearly 100% sensitive and specific. CT typically shows thickening of airways characterized by tram-track parallel lines or ring shadows representing thickened bronchial walls when imaged in cross-section. Cysts (sometimes appearing as grapelike clusters), scattered mucous plugs, and airways that are dilated > 1.5 times the diameter of nearby blood vessels can also be seen. Dilated medium-sized bronchi may extend almost to the pleurae. Atelectasis, consolidation, and decreased vascularity are nonspecific findings. A differential diagnosis of dilated airways includes bronchitis and traction bronchiectasis that occurs when pulmonary fibrosis pulls airways open.

Pulmonary function tests: Pulmonary function tests can be helpful for documenting baseline function and for following the progression of disease over time. Bronchiectasis causes airflow limitation (reduced forced expiratory volume in 1 sec [FEV_1], forced vital capacity [FVC], and FEV_1/FVC); the FEV_1 can improve in response to β-agonist bronchodilators. Lung volume measurements may be increased or decreased, and diffusing capacity for carbon monoxide (DLCO) may be decreased.

Diagnosis of cause: Tests to help diagnose a cause include sputum evaluation, including staining and cultures for bacterial, mycobacterial (*Mycobacterium avium* complex and *M. tuberculosis*), and fungal (*Aspergillus*) infection. Mycobacterial superinfection is diagnosed by repeatedly culturing mycobacteria other than TB in high colony counts and by finding granulomas on biopsy with concurrent radiologic evidence of disease. Additional tests may include the following:

• Sweat chloride testing to diagnose cystic fibrosis (which should be done even in older patients)

• Rheumatoid factor and other serologic tests to look for connective tissue diseases

• Immunoglobulin measurement (including IgG subclass determination), *Aspergillus* precipitins, IgE, and eosinophilia to rule out allergic bronchopulmonary aspergillosis

• α_1-Antitrypsin levels to document α_1-antitrypsin deficiency

When the clinical presentation suggests ciliary dyskinesia (by concurrent sinus disease and middle and lower lobe bronchiectasis with or without infertility), a nasal or bronchial epithelial sample should be obtained and examined by transmission electron microscopy for abnormal ciliary structure. A less invasive alternative is examination of sperm motility. The diagnosis of ciliary dyskinesia should be made cautiously by an experienced physician trained in specialized electron microscopic techniques because nonspecific structural defects can be present in up to 10% of cilia in healthy patients and in patients with pulmonary disease; infection can cause transient dyskinesia; and ciliary ultrastructure may be normal in patients with primary ciliary dyskinesia syndromes characterized by abnormal ciliary function.

Bronchoscopy is indicated when an anatomic or an obstructing object or lesion is suspected.

Prognosis

Overall, prognosis is thought to be good, with about 80% of patients having no further deterioration of lung function on the basis of bronchiectasis alone. However, cystic fibrosis patients have a median survival of 36 yr, and most patients continue to have intermittent acute exacerbations.

Treatment

• Prevention of exacerbations with antibiotics and regular vaccinations

• Measures to help clear secretions

• Antibiotics for acute exacerbations

• Sometimes surgical resection

There is no consensus on the best approach to prevent or limit acute exacerbations. Options include daily prophylactic oral antibiotics (eg, ciprofloxacin 500 mg bid) and, in patients who have cystic fibrosis and are colonized with *P. aeruginosa*, inhaled tobramycin (300 mg bid every other month). In patients with diffuse bronchiectasis due to other causes, aerosolized gentamicin (40 mg bid) may also be effective. Chronic therapy with azithromycin 500 mg po 3 times/wk has demonstrated efficacy in patients with cystic fibrosis; it is unclear whether macrolides are useful in other patients. The mechanism of this effect is not known and may not be due to antibiotic effect.

As with all patients with chronic pulmonary disease, annual vaccination against influenza and vaccination every 5 yr against pneumococcus is recommended.

Various techniques can facilitate clearance of secretions, including postural drainage and chest percussion, positive expiratory pressure devices, intrapulmonary percussive ventilators, pneumatic vests, and autogenic drainage (a breathing technique thought to help move secretions from peripheral to central airways). Nebulized drugs, including a mucolytic (rhDNase) or hypertonic (7%) saline, have clinical utility in patients with cystic fibrosis. Patients should be introduced to these techniques by a respiratory therapist and should use whichever technique is most effective for them because no evidence favors one technique.

Additional treatment depends on the cause. For cystic fibrosis, see p. 2881. Allergic bronchopulmonary aspergillosis is treated with corticosteroids and possibly with azole antifungals (see p. 1888). Patients with immunoglobulin or α_1-antitrypsin deficiencies should receive replacement therapy.

Acute exacerbations: Acute exacerbations are treated with antibiotics and increased efforts to clear sputum from the airways with the use of bronchodilators and mucolytics. Inflammation may be treated with inhaled or oral corticosteroids. Antibiotic choice depends on whether patients have cystic fibrosis or non-cystic fibrosis bronchiectasis.

Antibiotics for non-cystic fibrosis bronchiectasis should initially cover *H. influenzae*, *P. aeruginosa*, *M. catarrhalis*, *S. aureus*, and *S. pneumoniae* (eg, ciprofloxacin 500 mg po bid or levofloxacin 500 mg po once/day for 7 to 14 days) and should be adjusted according to culture results.

Antibiotic selection for cystic fibrosis exacerbations is guided by sputum culture. Routine annual sputum cultures should be done on all patients with cystic fibrosis. During childhood, common infecting organisms are *S. aureus* and *H. influenzae* and quinolone antibiotics such as ciprofloxacin and levofloxacin may be used. In the later stages of cystic fibrosis, infections involve highly resistant strains of certain gram-negative organisms including *P. aeruginosa*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. In these patients, treatment is with multiple antibiotics (eg, tobramycin, aztreonam, ticarcillin/clavulanate, ceftazidime, cefepime). IV administration is frequently required.

Complications: Significant hemoptysis is usually treated with bronchial artery embolization, but surgical resection may be considered if pulmonary function is adequate.

Superinfection with mycobacterial organisms such as *M. avium* complex almost always requires multiple drug regimens that include clarithromycin 500 mg po bid or azithromycin 250 mg once/day; rifampin 600 mg po once/day or rifabutin 300 mg po once/day; and ethambutol 25 mg/kg po once/day for 2 mo followed by 15 mg/kg once/day. Drug therapy is modified based on culture and sensitivity results. All drugs should be taken until sputum cultures have been negative for 12 mo.

Surgical resection for localized bronchiectasis is rarely needed but is considered when medical therapy has been optimized and the symptoms are intolerable. In certain patients with diffuse bronchiectasis, lung transplantation is also an option. Five-year survival rates as high as 65 to 75% have been reported when a heart-lung or double lung transplantation is done. Pulmonary function usually improves within 6 mo, and the improvement may be sustained for at least 5 yr.

Chapter 199. Interstitial Lung Diseases

Introduction

(Diffuse Parenchymal Lung Diseases)

Interstitial lung diseases are a heterogeneous group of disorders characterized by alveolar septal thickening, fibroblast proliferation, collagen deposition, and, if the process remains unchecked, pulmonary fibrosis. Interstitial lung diseases can be classified using various criteria (eg, acute vs chronic, granulomatous vs nongranulomatous, known cause vs unknown cause, primary lung disease vs secondary to systemic disease).

Among the numerous possible causes are most connective tissue disorders and occupational lung exposures and many drugs (see Table 199-1 and also Ch. 201). A number of interstitial diseases of unknown etiology have characteristic histology, clinical features, or presentation

[**Table 199-1.** Causes of Interstitial Lung Disease]

and thus are considered unique diseases, including eosinophilic pulmonary diseases, pulmonary Langerhans' cell granulomatosis (histiocytosis), lymphangioleiomyomatosis, pulmonary alveolar proteinosis, and sarcoidosis. In up to 30% of patients who have interstitial diseases with no clear cause, the processes are distinguished primarily by characteristic histopathologic features; these processes are termed the idiopathic interstitial pneumonias.

Idiopathic Interstitial Pneumonias

Idiopathic interstitial pneumonias (IIPs) are interstitial lung diseases of unknown etiology that share similar clinical and radiologic features and are distinguished primarily by the histopathologic patterns on lung biopsy. Classified into 6 histologic subtypes, all are characterized by varying degrees of inflammation and fibrosis and all cause dyspnea. Diagnosis is based on history, physical examination, imaging, pulmonary function tests, and lung biopsy. Treatment varies by subtype but typically involves corticosteroids, cytotoxic drugs, or both; treatment is frequently ineffective. Prognosis varies by subtype and ranges from excellent to nearly always fatal.

The 6 histologic subtypes of IIP in decreasing order of frequency are

- Usual interstitial pneumonia, known clinically as idiopathic pulmonary fibrosis
- Nonspecific interstitial pneumonia
- Cryptogenic organizing pneumonia
- Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
- Desquamative interstitial pneumonia
- Acute interstitial pneumonia

These subtypes are characterized by varying degrees of interstitial inflammation and fibrosis. All cause dyspnea; diffuse usually reticular opacities on chest x-ray; and inflammation, fibrosis, or both on biopsy. The subtypes are important to distinguish, however, because they have different clinical features (see Table 199-2) and respond differently to treatment. Lymphoid interstitial pneumonia, although still considered a subtype of IIP, is now thought to be part of the lymphoproliferative disease spectrum rather than a primary interstitial lung disease (see p. 1961).

Symptoms and Signs

Symptoms and signs are usually nonspecific. Cough and dyspnea on exertion are typical, with variable onset and progression. Common signs include tachypnea, reduced chest expansion, and bibasilar end-inspiratory dry crackles.

Diagnosis

• Chest x-ray

• High-resolution CT (HRCT)

• Pulmonary function tests

• Lung biopsy

IIP should be suspected in any patient with unexplained interstitial lung disease. Clinicians, radiologists, and pathologists should exchange information to determine the diagnosis in individual patients. Potential causes (see Table 199-1) are assessed systematically. For maximum diagnostic yield, history should address the following criteria:

• Symptom duration

• Family history of lung disease, especially lung fibrosis

• History of tobacco use (because some diseases occur mostly among current or former smokers)

• Current and prior drug use

• Detailed review of home and work environments, including those of family members. A chronologic listing of the patient's entire employment history, including specific duties and known exposures to dusts, gases, and chemicals, is obtained. The degree of exposure, duration of exposure, latency of exposure, and the use of protective devices is elicited.

Chest x-rays are always done as are pulmonary function tests (see p. 1851). HRCT, which distinguishes airspace from interstitial disease, provides better assessment of the extent and distribution of disease and is more likely to detect underlying or coexisting disease (eg, occult mediastinal adenopathy, cancer, emphysema). HRCT is best done with the patient prone to reduce dependent lung atelectasis.

The initial laboratory evaluation includes liver and renal function tests and CBC to check for anemia, polycythemia, and leukocytosis. Other tests are done for patients who have clinical features suggesting a connective tissue disorder, vasculitis, or environmental exposure. Such tests include ESR, antinuclear antibodies, rheumatoid factor, hypersensitivity panel (a collection of tests for antibodies to common antigens from microbial, fungal, and animal sources), antineutrophil cytoplasmic antibodies, and anti-basement membrane antibody.

Bronchoscopic transbronchial biopsy can exclude interstitial lung disease, establishing

[**Table 199-2.** Key Features of Idiopathic Interstitial Pneumonias*]

a diagnosis of another disorder, but the biopsy does not yield enough tissue to diagnose one of the IIPs. Bronchoalveolar lavage helps narrow the differential diagnosis in some patients and can provide information about disease progression and response to therapy. The usefulness of this procedure in the initial clinical assessment and follow-up of most patients with these diseases has not been established, however.

Surgical lung biopsy is usually needed to confirm the diagnosis except when HRCT shows a pattern consistent with idiopathic pulmonary fibrosis. Biopsy of multiple sites with an open or video-assisted thoracoscopic surgery (VATS) procedure is required.

Treatment

Treatment may vary by disorder (see Table 199-3). Smoking cessation is always recommended to avoid accelerating disease progression. Corticosteroids are recommended for cryptogenic organizing pneumonia, lymphoid interstitial pneumonia, and nonspecific interstitial pneumonia. Lung transplantation may be recommended for end-stage disorders.

Idiopathic Pulmonary Fibrosis

(Cryptogenic Fibrosing Alveolitis)

Idiopathic pulmonary fibrosis (IPF), the most common form of IIP, causes progressive pulmonary fibrosis predominantly in male smokers. Symptoms and signs develop over months to years and include exertional dyspnea, cough, and fine (Velcro) crackles. Diagnosis is based on history, physical examination, chest x-ray, and pulmonary function tests and is confirmed with HRCT, lung biopsy, or both if necessary. No specific treatment has proved effective. Most patients deteriorate; median survival is < 3 yr from diagnosis.

IPF, identified histologically as usual interstitial pneumonia, accounts for about 50% of cases of IIP. IPF affects men and women in their 50s and 60s in a ratio of 2:1. Current or former cigarette smoking is most strongly associated with the disease. There is some genetic predisposition; familial clustering occurs in up to 3% of cases.

Etiology

Environmental, genetic, or other unknown factors are thought to initially trigger alveolar epithelial cell injury, but self-perpetuating

[**Table 199-3.** Treatment and Prognosis of Idiopathic Interstitial Pneumonias*]

and aberrant interstitial fibroblast and mesenchymal cell proliferation (with collagen deposition and fibrosis) are thought to account for development of clinical disease.

Pathophysiology

The key histologic findings are subpleural fibrosis with sites of fibroblast proliferation (fibroblast foci) and dense scarring, alternating with areas of normal lung tissue (heterogeneity). Scattered interstitial inflammation occurs with lymphocyte, plasma cell, and histiocyte infiltration. Cystic dilatation of peripheral alveoli (honeycombing) occurs in all patients and increases with advanced disease. A similar histologic pattern uncommonly occurs in cases of interstitial lung diseases of known etiology (see Table 199-2).

Symptoms and Signs

Symptoms and signs typically develop over 6 mo to several years and include dyspnea on exertion and nonproductive cough. Constitutional symptoms, such as low-grade fever and myalgias, are uncommon. The classic sign of IPF is fine, dry, bibasilar inspiratory crackles (Velcro crackles). Clubbing is present in about 50% of cases. The remainder of the examination is normal until disease is advanced, at which time signs of pulmonary hypertension and right ventricular systolic dysfunction may develop.

Diagnosis

- HRCT
- Pulmonary function tests
- Often surgical lung biopsy

Diagnosis is suspected in patients with subacute dyspnea, nonproductive cough, and Velcro crackles on chest examination. However, IPF is commonly overlooked initially because of clinical similarities to other more common diseases, such as bronchitis, asthma, and heart failure. Diagnosis requires HRCT, pulmonary function tests, and often surgical lung biopsy.

Chest x-ray typically shows diffuse reticular opacities in the lower and peripheral lung zones. Small cystic lesions (honeycombing) and dilated airways due to traction bronchiectasis are additional findings.

Pulmonary function tests typically reveal a restrictive pattern (see p. 1855). Diffusing capacity for carbon monoxide (DLCO) is also reduced. ABGs show hypoxemia, which is often exaggerated or elicited by exercise and low arterial CO_2 levels.

HRCT shows diffuse, patchy, subpleural, reticular opacities with irregularly thickened interlobular septa and intralobular lines; subpleural honeycombing; and traction bronchiectasis. Ground-glass opacities affecting > 30% of the lung suggest an alternative diagnosis.

Laboratory testing plays little role in diagnosis.

Prognosis

Most patients have moderate to advanced clinical disease at the time of diagnosis and deteriorate despite treatment. Normal PaO_2 at presentation and fewer fibroblastic foci on biopsy predict a better prognosis. Prognosis is worse with advanced age, poor pulmonary function at presentation (forced vital capacity [FVC] < 55% of predicted or DLCO < 35% of predicted), and severe dyspnea. Median survival is < 3 yr from time of diagnosis.

Causes of acute deterioration include infections, pulmonary embolism, pneumothorax, and heart failure. Also, acute exacerbations without an identifiable cause are common and have a high morbidity. Lung cancer occurs more frequently in patients with IPF, but cause of death is usually respiratory failure, respiratory infection, or heart failure with ischemia and arrhythmia. Because of the poor prognosis of IPF, discussions with the patient and family about advance care planning and end-of-life care are important at the early stages of diagnosis and management (see p. 3471).

Treatment

• Supportive care

• Possibly corticosteroids and immunosuppressants

• Sometimes lung transplantation

No specific treatment has proved effective. Supportive therapy consists of O_2 for hypoxemia, pulmonary rehabilitation, and antibiotics for pneumonias. Smoking must be stopped. Joining a support group may help reduce the stress of the illness. Treatment of IPF with corticosteroids and cytotoxic agents is of unproven benefit and causes substantial morbidity; thus, combined therapy should not be routinely prescribed. Drugs such as *N*-acetylcysteine, bosentan, pirfenidone, warfarin, and etanercept show promise, but there is insufficient evidence to recommend their general use.

Lung transplantation is successful for otherwise healthy IPF patients < 55 yr with end-stage pulmonary disease (< 40% of all IPF patients). Otherwise healthy IPF patients should be evaluated for lung transplantation at the time of diagnosis.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia is an idiopathic interstitial pneumonia that occurs mainly in women, nonsmokers, and patients < 50 yr.

Idiopathic nonspecific interstitial pneumonia is the second most common idiopathic interstitial pneumonia. Most patients are between the ages of 40 and 50 and have no known cause or association. However, a similar pathologic process can occur in patients with a connective tissue disorder (in particular, systemic sclerosis or polymyositis/dermatomyositis), in some forms of drug-induced lung injury, and in patients with hypersensitivity pneumonitis.

Clinical presentation is similar to that of IPF. Cough and dyspnea are present for months to years. Constitutional symptoms are unusual, although a low-grade fever and malaise are possible.

Diagnosis

• HRCT

• Pulmonary function tests

• Biopsy

The diagnosis should be considered in patients with unexplained subacute or chronic cough and dyspnea. Diagnosis usually requires chest x-ray, HRCT, pulmonary function tests, and biopsy. In contrast to idiopathic pulmonary fibrosis, antinuclear antibodies and rheumatoid factor may be positive in low titer.

Pulmonary function tests usually show a restrictive pattern. Hypoxemia is often present at rest and is even more prominent with exercise.

Chest x-ray primarily shows lower-zone reticular opacities. Bilateral patchy opacities are also possible. HRCT findings include bilateral patchy ground-glass attenuation, bilateral areas of consolidation, irregular lines, and bronchial dilatation. Ground-glass attenuation is the predominant finding in most cases and is the sole abnormality in about one third of cases. More than half of patients have an increased percentage of lymphocytes in bronchoalveolar lavage fluid.

The main histologic feature of nonspecific interstitial pneumonia is homogenous inflammation and fibrosis, as opposed to the heterogeneity in usual interstitial pneumonia. The changes are temporally uniform, but the process may be patchy, with intervening areas of unaffected lung. Honeycomb areas are rare.

Treatment

• Corticosteroids

Most patients respond to corticosteroids. Relapse may occur. The disease progresses in a small percentage of patients and these die 5 to 10 yr after diagnosis. The estimated overall 10-yr mortality is < 15 to 20%.

Cryptogenic Organizing Pneumonia

(Bronchiolitis Obliterans Organizing Pneumonia)

Cryptogenic organizing pneumonia (COP) is an idiopathic condition in which granulation tissue obstructs alveolar ducts and alveolar spaces with chronic inflammation occurring in adjacent alveoli.

COP affects men and women equally, usually in their 40s or 50s. Cigarette smoking does not seem to be a risk factor.

About one half of patients recall having a community-acquired pneumonia-like syndrome (ie, a nonresolving flu-like illness characterized by cough, fever, malaise, fatigue, and weight loss) at the onset of the illness. Progressive cough and exertional dyspnea are what usually prompt the patient to seek medical attention. Chest examination demonstrates Velcro crackles.

Diagnosis

• HRCT

• Pulmonary function tests

• Often biopsy

Diagnosis requires imaging tests, pulmonary function tests, and, if the diagnosis is not clear from these tests, biopsy. Chest x-ray shows bilateral, diffuse, peripherally distributed alveolar opacities with normal lung volumes; a peripheral distribution similar to chronic eosinophilic pneumonia may occur. Rarely, alveolar opacities are unilateral. Recurrent and migratory pulmonary opacities are common. Rarely, irregular linear or nodular interstitial opacities or honeycombing are visible at presentation. HRCT of the lung shows patchy airspace consolidation (present in 90% of patients), ground-glass opacities, small nodular opacities, and bronchial wall thickening and dilatation. The patchy opacities are more common in the periphery of the lung, often in the lower lung zone. CT may show much more extensive disease than is expected from review of the chest x-ray.

Pulmonary function tests usually show a restrictive defect, although an obstructive defect (ratio of forced expiratory volume in 1 sec to forced vital capacity [FEV_1/FVC] < 70%) is found in 21% of patients, and pulmonary function is occasionally normal. Hypoxemia during rest and exercise is common.

Routine laboratory test results are nonspecific. Leukocytosis without an increase in eosinophils occurs in about one half of patients. The initial ESR often is elevated.

Lung biopsy shows excessive proliferation of granulation tissue within small airways and alveolar ducts, with chronic inflammation in the surrounding alveoli. Foci of organizing pneumonia are nonspecific and can occur secondary to other pathologic processes, including infections, Wegener's granulomatosis, lymphoma, hypersensitivity pneumonitis, and eosinophilic pneumonia.

Treatment

• Corticosteroids

Clinical recovery follows treatment with corticosteroids in two thirds of patients, often within 2 wk. Relapses occur in up to 50% of patients, but these patients are responsive to additional courses of corticosteroids. Recovery after treatment is common when COP appears on HRCT as parenchymal consolidation, ground-glass opacity, or nodules. In contrast, recovery is less common when COP appears on HRCT as linear and reticular opacities.

Respiratory Bronchiolitis-Associated Interstitial Lung Disease

Respiratory bronchiolitis-associated interstitial lung disease (RBILD) is a syndrome of small airway inflammation and interstitial lung disease occurring in smokers.

Most smokers develop a subclinical bronchiolitis characterized by mild or moderate inflammation of the small airways. The few patients who develop more severe inflammation with clinically significant interstitial disease are said to have RBILD. Male-to-female ratio is 2:1. RBILD is characterized histologically by submucosal inflammation of the membranous and respiratory bronchioles manifested by the presence of tan-brown pigmented macrophages (resulting from increased iron content, as occurs in smokers), mucus stasis, and metaplastic cuboidal epithelium in bronchioles and alveoli. Alveolar septal scarring always occurs. Similar findings, however, occur in some hypersensitivity reactions, occupational lung exposures (usually due to mineral dusts), viral infections, and drug reactions. RBILD also resembles desquamative interstitial pneumonia histologically, but in RBILD inflammation is patchier and less extensive. The similarity of the 2 conditions has led to the suggestion that they are different manifestations of the same disease caused by cigarette smoking.

Symptoms of cough and breathlessness with exertion resemble those of other interstitial lung diseases, especially idiopathic pulmonary fibrosis, but are milder. Crackles on examination are the only physical finding.

Diagnosis

• Chest x-ray, CT

• Pulmonary function tests

Diagnosis is considered in patients being evaluated for interstitial lung disease. Diagnostic testing includes imaging tests, pulmonary function tests, and biopsy. Chest x-ray findings include the following:

• Diffuse, fine reticular or nodular opacities

• Bronchial wall thickening

• Prominent peribronchovascular interstitium

• Small regular and irregular opacities

• Small peripheral ring shadows

HRCT often shows attenuation nodules and patchy areas of hazy ground-glass opacities. A mixed obstructive-restrictive pattern is common on pulmonary function tests, although results may be normal or show an isolated increase in residual volume. ABG measurements show mild hypoxemia. Routine laboratory tests are not helpful.

Treatment

• Smoking cessation

Treatment is smoking cessation and avoidance of even passive cigarette smoke exposure, which may prevent improvement or lead to recurrence of the illness. There is only anecdotal evidence of the efficacy of corticosteroids. The natural clinical course of the disease is unknown, but prognosis is good with smoking cessation.

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia is chronic lung inflammation characterized by mononuclear cell infiltration of the airspaces; it occurs almost exclusively in current or former cigarette smokers.

Over 90% of patients with desquamative interstitial pneumonia are smokers, who tend to develop the disease in their 30s or 40s. The disease tends to affect the lung parenchyma uniformly. The alveolar walls are lined with plump cuboidal pneumocytes; there is moderate infiltration of the alveolar septum by lymphocytes, plasma cells, and, occasionally, eosinophils. Alveolar septal fibrosis, if present, is mild. The most striking feature is the presence of numerous pigmented macrophages within distal airspaces, mistaken as desquamated pneumocytes when the disease was first described. Honeycombing is rare. Similar but much less extensive findings occur in RBILD, leading to the suggestion that desquamative interstitial pneumonia and RBILD are different manifestations of the same disease caused by cigarette smoking.

Diagnosis

• Chest x-ray, CT

Chest x-ray abnormalities include bibasilar hazy opacities without honeycombing; findings may be normal

in up to 20% of cases. HRCT shows multifocal or diffuse, basilar, subpleural ground-glass opacities. Irregular linear and reticular opacities are common but are not usually the dominant features. Honeycombing may be visible, occurs in the minority of patients, and is usually limited.

Treatment

• Smoking cessation

• Sometimes corticosteroids or cytotoxic drugs

Smoking cessation results in clinical improvement in an estimated 75% of patients. Patients who do not improve may respond to corticosteroids or cytotoxic drugs. Prognosis is good, with about 70% survival at 10 yr.

Acute Interstitial Pneumonia

(Accelerated Interstitial Pneumonia; Hamman-Rich Syndrome)

Acute interstitial pneumonia (AIP) is an idiopathic version of acute respiratory distress syndrome (ARDS—see p. 2284).

AIP equally affects apparently healthy men and women usually > 40 yr.

AIP is defined histologically by organizing diffuse alveolar damage, a nonspecific pattern that occurs in other causes of lung injury unrelated to IIP. The hallmark of organizing diffuse alveolar damage is diffuse, marked alveolar septal edema with inflammatory cell infiltration; fibroblast proliferation; occasional hyaline membranes; and thickening of the alveolar walls. Septa are lined with atypical, hyperplastic type II pneumocytes, and airspaces are collapsed. Thrombi develop in small arteries but are nonspecific.

Symptoms consist of the abrupt onset of fever, cough, and shortness of breath, which in most patients increase in severity over 7 to 14 days, progressing to respiratory failure.

Diagnosis is suspected in patients with symptoms, signs, and chest x-ray findings of ARDS (eg, diffuse bilateral airspace opacification). Diagnosis is supported by HRCT but usually requires biopsy. HRCT shows bilateral patchy symmetric areas of ground-glass attenuation and sometimes bilateral areas of airspace consolidation in a predominantly subpleural distribution. Mild honeycombing, usually affecting < 10% of the lung, may be present. Routine laboratory tests are nonspecific and generally not helpful.

Diagnosis is confirmed by surgical lung biopsy showing diffuse alveolar damage in the absence of known causes of ARDS and diffuse alveolar damage (eg, sepsis, drugs, toxins, radiation, viral infection). Biopsy is often required to distinguish AIP from diffuse alveolar hemorrhage syndrome, acute eosinophilic pneumonia, and cryptogenic organizing pneumonia.

Treatment is supportive and usually requires mechanical ventilation. Corticosteroid therapy is generally used, but efficacy has not been established.

Mortality is > 60%; most patients die within 6 mo of presentation, and death is usually due to respiratory failure. Patients who survive the initial acute episode may recover complete pulmonary function, although the disease may recur.

Drug-Induced Pulmonary Disease

Drug-induced pulmonary disease is not a single disorder, but rather a common clinical problem in which a patient without previous pulmonary disease develops respiratory symptoms, chest x-ray changes, deterioration of pulmonary function, histologic changes, or several of these findings in association with drug therapy. Over 150 drugs or categories of drugs have been reported to cause pulmonary disease; the mechanism is rarely known, but many drugs are thought to provoke a hypersensitivity response. Some drugs (eg, nitrofurantoin) can cause different injury patterns in different patients.

Depending on the drug, drug-induced syndromes can cause interstitial fibrosis, organizing pneumonia, asthma, noncardiogenic pulmonary edema, pleural effusions, pulmonary eosinophilia, pulmonary hemorrhage, or veno-occlusive disease (see Table 199-4).

Diagnosis is based on observation of responses to withdrawal from and, if practical, reintroduction to the suspected drug.

Treatment is stopping the drug. A screening pulmonary function test is commonly done in patients about to begin or already taking drugs with pulmonary toxicities, but the benefits of screening for prediction or early detection of toxicity are unproved.

Eosinophilic Pulmonary Diseases

Eosinophilic pulmonary diseases are a heterogeneous group of disorders characterized by the accumulation of eosinophils in alveolar spaces, the interstitium, or both. Peripheral blood eosinophilia is also common. Known causes of eosinophilic pulmonary disease include

• Infections (especially helminthic infections)

• Drug-induced pneumonitis (eg, antibiotics, phenytoin, L-tryptophan)

• Inhaled toxins (eg, cocaine)

• Systemic disorders (eg, Churg-Strauss syndrome)

• Allergic bronchopulmonary aspergillosis

Often the cause is unknown.

Diagnosis is based on demonstration of opacities on chest x-ray and identification of eosinophilia (> 450/μL) in peripheral blood, bronchoalveolar lavage fluid, or lung biopsy tissue. However, pulmonary eosinophilia may occur in the absence of peripheral eosinophilia.

[**Table 199-4.** Substances with Toxic Pulmonary Effects]

Pulmonary opacities on chest x-ray associated with blood eosinophilia are sometimes called PIE (pulmonary infiltrates with eosinophilia) syndrome.

Eosinophils are primarily tissue-dwelling and are several hundred-fold more abundant in tissues than in blood. Consequently, blood eosinophil numbers do not necessarily indicate the extent of eosinophilic involvement in affected tissues. Eosinophils are most numerous in tissues with a mucosal epithelial interface with the environment, such as the respiratory, GI, and lower GU tracts. Eosinophils are not present in the lungs of healthy people, so their presence in tissue or bronchoalveolar lavage fluid (> 5% of differential count) identifies a pathologic process.

Eosinophils are exquisitely sensitive to corticosteroids and completely disappear from the bloodstream within a few hours after administration of corticosteroids. This rapid disappearance from the blood may obscure the diagnosis in patients who receive corticosteroids before the diagnostic assessment is instituted.

The two primary eosinophilic pulmonary diseases of unknown etiology are chronic and acute eosinophilic pneumonia. Hypereosinophilic syndrome, a systemic disease affecting multiple organs, is discussed elsewhere (see p. 990).

Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia (CEP) is a disorder of unknown etiology characterized by an abnormal, chronic accumulation of eosinophils in the lung.

CEP is not truly chronic; rather it is an acute or subacute illness that recurs (thus, a better name might be recurrent eosinophilic pneumonia). The prevalence and incidence of CEP are unknown. Etiology is suspected to be an allergic diathesis. Most patients are nonsmokers.

Symptoms and Signs

Patients often present with fulminant illness characterized by cough, fever, progressive breathlessness, wheezing, and night sweats. The clinical presentation may suggest a community-acquired pneumonia. Asthma accompanies or precedes the illness in > 50% of cases. Those with recurrent symptoms may have weight loss.

Diagnosis

• Chest x-ray

• Exclusion of infectious causes of pneumonia

Diagnosis is suspected in patients with characteristic symptoms and typical radiographic appearance. Diagnosis also requires CBC, ESR, sometimes iron studies, and exclusion of infectious causes by appropriate cultures (see p. 3471). Peripheral blood eosinophilia, a very high ESR, iron deficiency anemia, and thrombocytosis are all frequently present. Chest x-ray findings of bilateral peripheral or pleural-based opacities, most commonly in the middle and upper lung zones, is described as the photographic negative of pulmonary edema and is virtually pathognomonic (although present in < 25% of patients). A similar pattern is present on CT in virtually all cases. Bronchoalveolar lavage and biopsy are almost always done. Eosinophilia > 40% in bronchoalveolar lavage fluid is suggestive of CEP; serial bronchoalveolar lavage examinations may help document the course of disease. Biopsy shows interstitial and alveolar eosinophils and histiocytes, including multinucleated giant cells, and organizing pneumonia. Fibrosis is minimal.

Treatment

• Systemic corticosteroids

• Sometimes maintenance therapy with inhaled corticosteroids, oral corticosteroids, or both

Patients with CEP are uniformly responsive to IV or oral corticosteroids; failure to respond suggests another diagnosis. Initial treatment is prednisone 40 to 60 mg once/day. Clinical improvement is often striking and rapid, often occurring within 48 h. Complete resolution of symptoms and x-ray abnormalities occurs within 14 days in most patients and by 1 mo in almost all. Symptoms and plain chest x-rays are both reliable and efficient guides to therapy. Although CT is more sensitive for the detection of radiographic abnormalities, there is no benefit gained by repeating it. Peripheral eosinophil counts, ESR, and IgE levels can also be used to follow the clinical course during treatment. However, not all patients have abnormal laboratory test results.

Symptomatic or radiographic relapse occurs in 50 to 80% of cases either after cessation of therapy or, less commonly, with tapering of the corticosteroid dose. Relapse can occur months to years after the initial episode. Thus, corticosteroid therapy is occasionally continued indefinitely. Inhaled corticosteroids (eg, fluticasone or beclomethasone 500 to 750 µg bid) appear to be effective, especially in reducing the maintenance dose of oral corticosteroid.

Relapse does not appear to indicate treatment failure, a worse prognosis, or greater morbidity. Patients continue to respond to corticosteroids as during the initial episode. Fixed airflow obstruction can occur in some patients who recover, but the abnormalities are usually of borderline clinical significance.

CEP occasionally leads to physiologically important restrictive lung function abnormalities as a result of

irreversible fibrosis, but abnormalities are usually mild enough that CEP is an extremely unusual cause of morbidity or death.

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia (AEP) is a disorder of unknown etiology characterized by rapid eosinophilic infiltration of the lung interstitium.

In contrast to CEP, AEP is an acute illness that occurs once and does not recur. Incidence and prevalence are unknown. AEP can occur at any age but most often affects patients between 20 and 40 yr, with a male-to-female ratio of 21:1. The cause is unknown, but AEP may be an acute hypersensitivity reaction to an unidentified inhaled antigen in an otherwise healthy person. Cigarette or other smoke exposure may be involved.

Symptoms and Signs

AEP causes an acute febrile illness of short duration (usually < 7 days). Symptoms are nonproductive cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain. Signs include tachypnea, fever (often > 38.5° C), and bibasilar inspiratory crackles and, occasionally, rhonchi on forced exhalation. Patients with AEP frequently present with acute respiratory failure requiring mechanical ventilation. Rarely, distributive (hyperdynamic) shock can occur.

Diagnosis

• HRCT

• Usually CBC, pleural fluid analysis, and pulmonary function testing

• Bronchoscopy

The diagnosis is suspected in patients with symptoms of acute pneumonia that progresses to respiratory failure and does not respond to antibiotics. Diagnosis is based on findings from routine testing and is confirmed by bronchoscopy. AEP is a diagnosis of exclusion and requires the absence of known causes of eosinophilic pneumonia (eg, drug- and toxininduced, helminthic and fungal infection-related, Churg-Strauss syndrome, idiopathic hypereosinophilic syndrome, tumors). The CBC in most patients demonstrates markedly elevated eosinophil counts. ESR and IgE levels are high but are nonspecific.

The chest x-ray initially may show only subtle reticular or ground-glass opacities, often with Kerley B lines. Isolated alveolar (about 25% of cases) or reticular (about 25% of cases) opacities may also be observed. The pattern is unlike that occurring in chronic eosinophilic pneumonia, in which the opacities are localized to the lung periphery. Small pleural effusions occur in two thirds of patients and are frequently bilateral.

HRCT is always abnormal with bilateral, random, patchy ground-glass or reticular opacities.

Pleural fluid examination shows marked eosinophilia with high pH. Pulmonary function tests often show a restrictive process with reduced diffusing capacity for carbon monoxide (DLCO).

Bronchoscopy should be done for lavage and, occasionally, biopsy. Bronchoalveolar lavage fluid often shows a high number and percentage (> 25%) of eosinophils. The most common histopathologic features on biopsy include eosinophilic infiltration with acute and organizing diffuse alveolar damage, but few patients have undergone lung biopsy.

Treatment

• Systemic corticosteroids

Some patients improve spontaneously. Most are treated with prednisone 40 to 60 mg po once/day. In

patients with respiratory failure, methylprednisolone 60 to 125 mg IV q 6 h is preferred. The prognosis is excellent; response to corticosteroids and complete recovery without recurrence is almost universal. Pleural effusions resolve more slowly than parenchymal opacities.

Loffler's Syndrome

Loffler's syndrome is characterized by absent or mild respiratory symptoms (most often dry cough), fleeting migratory pulmonary opacities, and peripheral blood eosinophilia. Parasitic infections, especially *Ascaris lumbricoides*, may be the cause, but an identifiable etiologic agent is not found in up to one third of patients. The disease usually resolves within 1 mo. Treatment is symptomatic and consists of corticosteroids.

Hypersensitivity Pneumonitis

(Extrinsic Allergic Alveolitis)

Hypersensitivity pneumonitis is a syndrome of cough, dyspnea, and fatigue caused by sensitization and subsequent hypersensitivity to environmental (frequently occupational) antigens. Acute, subacute, and chronic forms exist; all are characterized by acute interstitial inflammation and development of granulomas and fibrosis with long-term exposure. Diagnosis is based on a combination of history, physical examination, imaging tests, bronchoalveolar lavage, and biopsy. Short-term treatment is with corticosteroids; long-term treatment is antigen avoidance.

Etiology

Over 300 antigens have been identified as triggers for hypersensitivity pneumonitis, although farming, birds, and water contamination account for about 75% of cases. Antigens are commonly categorized by type and occupation (see Table 199-5); farmer's lung, caused by inhalation of hay dust containing thermophilic actinomycetes, is the prototype. Substantial overlap exists between hypersensitivity pneumonitis and chronic bronchitis in farmers, in whom chronic bronchitis is far more common, occurs independently of smoking status, is linked to thermophilic actinomycete exposure, and leads to findings similar to those of hypersensitivity pneumonitis on diagnostic testing.

[**Table 199-5.** Examples of Hypersensitivity Pneumonitis]

Pathophysiololgy

The disorder seems to represent a type IV hypersensitivity reaction, in which repeated exposure to antigen in genetically susceptible people leads to acute neutrophilic and mononuclear alveolitis, followed by interstitial lymphocytic infiltration and granulomatous reaction. Fibrosis with bronchiolar obliteration occurs with continued exposure.

Circulating precipitins (antibodies sensitized to antigen) seem not to have a primary etiologic role, and clinical history of allergy (such as asthma and seasonal allergies) is not a predisposing factor. Cigarette smoking seems to delay or prevent development, perhaps through down-regulation of the lung's immune response to inhaled antigens. However, smoking may exacerbate the disease once established.

Hypersensitivity pneumonitis has clinical similarities to other disorders that have different pathophysiologies. Organic dust toxic syndrome (pulmonary mycotoxicosis, grain fever), for example, is a syndrome consisting of fever, chills, myalgias, and dyspnea that does not require prior sensitization and is thought to be caused by inhalation of toxins produced by fungi or other contaminants of organic dust. Silo filler's disease may lead to respiratory failure, acute respiratory distress syndrome (ARDS), and bronchiolitis obliterans or bronchitis but is caused by inhalation of toxic nitrogen oxides produced by freshly fermented corn or alfalfa silage. Occupational asthma causes dyspnea in people previously sensitized to an inhaled antigen, but features such as airflow obstruction, airway eosinophilia, and differences in triggering antigens distinguish it from hypersensitivity pneumonitis (see p. 1979).

Symptoms and Signs

Symptoms and signs tend to depend on whether onset is acute, subacute, or chronic. Only a small proportion of exposed people develop symptoms and in most cases only after weeks to months of exposure and sensitization.

Acute disease occurs in previously sensitized people with acute high-level antigen exposure and manifests as fever, chills, cough, bilateral vice-like chest tightness (as can occur in asthma), and dyspnea 4 to 8 h after exposure. Anorexia, nausea, and vomiting may also be present. Physical examination shows tachypnea, diffuse fine-to-medium inspiratory crackles, and, in almost all cases, absence of wheezing.

Chronic disease occurs in people with chronic low-level antigen exposure (such as owners of birds) and manifests as onset over months to years of exertional dyspnea, productive cough, fatigue, and weight loss. There are few physical findings; clubbing uncommonly occurs and fever is absent. In advanced cases, pulmonary fibrosis causes symptoms and signs of right heart failure, respiratory failure, or both.

Subacute disease falls between the acute and chronic forms and manifests either as cough, dyspnea, fatigue, and anorexia that develops over days to weeks or as acute superimposed on chronic symptoms.

Diagnosis

• Specific clinical criteria

• Chest x-ray and high-resolution CT (HRCT)

• Pulmonary function tests

• Bronchoalveolar lavage

• Histologic examination and serologic tests

Diagnosis requires a high index of suspicion in patients at risk and with compatible symptoms and a compatible occupational, avocational, or domestic exposure history. Chest x-ray, HRCT, and pulmonary function tests are done routinely. Bronchoalveolar lavage and biopsy may be necessary if results are inconclusive. Diagnosis is categorized as definite, probable, subclinical, or sensitization based on specific criteria (see Table 199-6). The differential diagnosis is broad and includes environmental pulmonary diseases (see Ch. 201), sarcoidosis, bronchiolitis obliterans, connective tissue-associated pulmonary disease, and other interstitial lung diseases.

[**Table 199-6.** Diagnostic Criteria for Hypersensitivity Pneumonitis]

Clues in the history include

• Recurring atypical pneumonias

• Symptom onset after moving to a new job or home

• A hot tub, a sauna, a swimming pool, or other sources of standing water or water damage in the home or regular exposure to them elsewhere

• Having birds as pets

• Exacerbation and relief of symptoms in and away from specific settings

Examination often is not useful in making the diagnosis, although abnormal lung sounds and clubbing may be present.

Imaging tests: Imaging tests are typically done for patients with appropriate history, symptoms, and signs.

Chest x-ray is neither sensitive nor specific for detecting disease and is frequently normal in patients with acute and subacute forms. It may show reticular or nodular opacities, usually when symptoms are present. Chest x-rays of patients with chronic disease are more likely to show reticular or nodular opacities in the upper lobes with reduced lung volumes and honeycombing, similar to that of idiopathic pulmonary fibrosis.

HRCT is far more likely to show abnormalities and is considered standard for evaluating parenchymal changes in hypersensitivity pneumonitis. The most typical HRCT finding is the presence of profuse, poorly defined centrilobular micronodules. These micronodules may be present in patients with acute, subacute, or chronic disease and, in the correct clinical context, strongly suggest hypersensitivity pneumonitis. Occasionally, ground-glass opacification (attenuation) is the predominant or only finding. It is usually diffuse but sometimes spares the periphery of the secondary lobule. Focal areas of hyperlucency, similar to those present in obliterative bronchiolitis, may be a prominent feature in some patients (eg, mosaic attenuation with air trapping on expiratory HRCT). In chronic hypersensitivity pneumonitis, there are findings of lung fibrosis (eg, lobar volume loss, linear or reticular opacities, or honeycombing). Some nonsmoking patients with chronic hypersensitivity pneumonitis have findings of upper lobe emphysema. Mediastinal lymphadenopathy is uncommon, thereby distinguishing hypersensitivity pneumonitis from sarcoidosis.

Pulmonary function tests: These should be done as part of the standard evaluation of suspected cases of hypersensitivity pneumonitis. The syndrome can cause obstructive, restrictive, or a mixed pattern of airway changes. Advanced disease most commonly causes a restrictive defect (decreased lung volumes), a decreased diffusing capacity for carbon monoxide (DLCO), and hypoxemia. Airway obstruction is unusual in acute disease but may develop in chronic disease.

Bronchoalveolar lavage: Results are rarely specific for the diagnosis but are often a component of the diagnostic assessment for chronic respiratory symptoms and pulmonary function abnormalities. A lymphocytosis in lavage fluid (> 60%) with $CD4^+/CD8^+$ ratio < 1.0 (the normal ratio ± standard error of the mean = 2.3 ± 0.2) is characteristic of the disorder; by contrast, lymphocytosis with $CD4^+$ predominance (ratio > 1.0) is more characteristic of sarcoidosis. Other findings may include mast cells > 1% (after acute exposure) and increased neutrophils and eosinophils.

Lymphocyte transformation testing is an in vitro test of sensitization and is particularly useful in detecting sensitization to metals. The test can be done on peripheral blood but is better done on bronchial lavage fluid. In this test, the patient's lymphocytes are exposed to potential antigens. If the lymphocytes transform into blasts and proliferate, they (and hence the patient) were previously sensitized to that antigen.

Lung biopsy: Biopsy is indicated when noninvasive testing is inconclusive. Transbronchial biopsy done through a bronchoscope is sufficient as long as multiple specimens are taken from areas of active disease and multiple sequential sections of tissue are examined histologically. Findings vary but include lymphocytic alveolitis, noncaseating granulomas, and granulomatosis. Interstitial fibrosis may be present but is usually mild in the absence of advanced radiographic changes.

Other tests: Additional testing is indicated when additional support for the diagnosis is required or to detect other causes of interstitial lung disease. Circulating precipitins (specific precipitating antibodies to the suspected antigen) are suggestive of an exposure that may be the cause of the illness. When combined with other criteria, they can be helpful diagnostically and avoid the need for biopsy. However, in isolation, presence of circulating precipitins is neither sensitive nor specific. Identification of a specific precipitating antigen may require detailed aerobiologic or microbiologic assessment or both of the workplace by industrial hygiene specialists, but workplace assessments usually are guided by known sources of inciting antigens (eg, *Bacillus subtilis* in detergent factories). Skin tests are not helpful, and eosinophilia is absent. Tests helpful in detecting other disorders include serologic tests and cultures (for psittacosis and other pneumonias) and autoantibodies (for collagen-vascular disease). Elevated

eosinophils may suggest chronic eosinophilic pneumonias. Hilar and paratracheal lymph node enlargement is more characteristic of sarcoidosis.

Prognosis

Pathologic changes are completely reversible if detected early and if antigen exposure is eliminated. Acute disease is self-limiting with antigen avoidance; symptoms usually lessen within hours. Chronic disease has a more complicated prognosis: fibrosis is usually irreversible but may not progress if the patient is no longer exposed to the antigen.

Treatment

• Corticosteroids

Treatment of acute or subacute hypersensitivity pneumonitis is with corticosteroids, usually prednisone 60 mg po once/day for 1 to 2 wk, then tapered over the next 2 to 4 wk to 20 mg once/day, followed by weekly decrements of 2.5 mg until the drug is stopped. This regimen relieves initial symptoms but does not appear to alter long-term outcome.

Prevention

The most important aspect of long-term management is avoidance of exposure to antigens. A complete change of environment is rarely realistic, especially for farmers and other workers, in which case dust control measures (such as wetting down compost before disturbing it) or using air filters or protective masks may be effective. Fungicides may be used to prevent the growth of antigenic microorganisms (eg, in hay or on sugar cane), but the long-term safety of this approach is unknown. Extensive cleaning of wet ventilation systems, removal of moist carpets, and maintenance of low humidity are also effective in some settings. Patients must be told, however, that these measures may be inadequate in the presence of continued exposure.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is nonmalignant growth of smooth muscle cells throughout the lung, pulmonary blood vessels, lymphatics, and pleurae. It is rare and occurs exclusively in young women. The cause is unknown. Symptoms are dyspnea, cough, chest pain, and hemoptysis; spontaneous pneumothorax is common. Diagnosis is suspected on the basis of symptoms and chest x-ray and is confirmed by high-resolution CT. Prognosis is uncertain, but the disorder is slowly progressive and over years often leads to respiratory failure and death. Primary treatment is lung transplantation.

LAM is not an interstitial lung disease, but patients are occasionally misdiagnosed as having interstitial lung disease (and also asthma or COPD).

LAM is a rare disease exclusive to women, typically affecting those between 20 and 40 yr. Whites are at greatest risk. LAM affects < 1 in 1 million people. It is characterized by nonmalignant proliferation of atypical smooth muscle cells throughout the chest, including lung parenchyma, vasculature, lymphatics, and pleurae, leading to distortion of lung architecture, cystic emphysema, and progressive deterioration of lung function.

Etiology

The cause of LAM is unknown. The tempting hypothesis that female sex hormones play a role in pathogenesis remains unproved. The disease usually arises spontaneously, but LAM bears many similarities to the pulmonary findings of tuberous sclerosis (TS—see p. 2905); LAM occurs in some patients with TS and is thought by some to be a forme fruste of TS. Mutations in the tuberous sclerosis complex-2 gene (*TSC-2*) have been described in LAM cells and angiomyolipomas (benign renal hamartomas made of smooth muscle, blood vessels, and adipose). Also, angiomyolipomas occur in up to 50% of patients with LAM. These observations suggest 1 of 2 possibilities: (1) somatic mosaicism for

TSC-2 mutations within the lungs and kidneys results in foci of disease superimposed against a background of normal cells within these tissues (although multiple discrete sites of disease might be expected) or (2) LAM represents dissemination of angiomyolipoma tissue to the lung in a fashion analogous to the syndrome of benign metastasizing leiomyoma.

Symptoms and Signs

Initial symptoms are dyspnea and, less commonly, cough, chest pain, and hemoptysis. There are few signs of disease, but some women have crackles and rhonchi. Many patients present with spontaneous pneumothorax. They may also present with manifestations of lymphatic obstruction, including chylothorax, chylous ascites, and chyluria. Symptoms are thought to worsen during pregnancy. Angiomyolipomas, although usually asymptomatic, can cause bleeding if they grow large (eg, > 4 cm), which usually presents as hematuria or flank pain.

Diagnosis

• Chest x-ray and high-resolution CT (HRCT)

• Lung biopsy if HRCT is nondiagnostic

Diagnosis is suspected in young women with dyspnea plus interstitial changes with normal or increased lung volumes on chest x-ray, spontaneous pneumothorax, or chylous effusion. HRCT is done in all patients suspected of having the disorder; findings of multiple, small, diffusely distributed cysts are generally pathognomonic for LAM.

Biopsy is indicated only when HRCT findings are nondiagnostic. Findings of an abnormal proliferation of smooth muscle cells (LAM cells) associated with cystic changes on histologic examination confirm disease.

Pulmonary function tests support the diagnosis and are especially useful for monitoring. Typical findings are of an obstructive or mixed obstructive and restrictive pattern. The lungs are usually hyperinflated with an increase in the total lung capacity (TLC) and thoracic gas volume. Gas trapping (an increase in residual volume [RV] and RV/TLC ratio) is commonly present. The PaO_2 and diffusing capacity for carbon monoxide (DLCO) are commonly reduced. Exercise performance is decreased in most patients.

Prognosis

Prognosis is unclear because the disorder is so rare and because the clinical course of patients with LAM is variable. In general, the disease is slowly progressive, leading eventually to respiratory failure and death, but the time to death varies widely among reports. Median survival is likely > 8 yr from diagnosis. Lung function declines 2 to 3 times faster than it does in healthy people. Women should be advised that progression may accelerate during pregnancy.

Treatment

• Lung transplantation

Standard treatment is lung transplantation, but the disorder can recur in transplanted lungs. Alternative treatments, such as hormonal manipulation with progestins, tamoxifen, and oophorectomy, are largely ineffective. Pneumothoraces may be difficult to manage because they are often recurrent, bilateral, and less responsive to standard measures. Recurrent pneumothorax requires pleural abrasion, talc or chemical pleurodesis, or pleurectomy. Embolization to prevent bleeding should be considered for angiomyolipomas > 4 cm.

Air travel is well-tolerated by most patients but may be contraindicated in those with

• New or worsening respiratory symptoms

• Prior pneumothorax or hemoptysis

• Evidence of extensive subpleural bullous or cystic changes on HRCT

Patients can receive education and psychologic support from the LAM Foundation in the US.

Lymphoid Interstitial Pneumonia

(Lymphocytic Interstitial Pneumonitis)

Lymphoid interstitial pneumonia (LIP) is lymphocytic infiltration of the alveolar interstitium and air spaces. The cause is unknown. It most often occurs in children with HIV infection and in people of any age with an autoimmune disorder. Symptoms and signs are cough, progressive dyspnea, and crackles. Diagnosis is based on history, physical examination, imaging tests, pulmonary function tests, and lung biopsy. Treatment is with corticosteroids, cytotoxic drugs, or both, although efficacy is unknown. Five-year survival is 50 to 66%.

LIP is a rare disorder characterized by infiltration of alveoli and alveolar septa with small lymphocytes and varying numbers of plasma cells. Noncaseating, poorly formed granulomas may be present but are usually rare and inconspicuous.

LIP is the most common cause of pulmonary disease after *Pneumocystis* infection in HIV-positive children and is the AIDS-defining illness in up to one half of HIV-positive children. LIP affects < 1% of adults with or without HIV infection. Women and girls are affected more commonly.

The cause is postulated to be an autoimmune disease or a nonspecific response to infection with Epstein-Barr virus, HIV, or other viruses. Evidence of an autoimmune etiology includes its frequent association with Sjogren's syndrome (25% of cases of LIP) and other diseases (eg, SLE, RA, Hashimoto's thyroiditis—14% of cases). Evidence of an indirect viral etiology includes frequent association with immunodeficient states (HIV/AIDS, combined variable immunodeficiency, agammaglobulinemia—14% of cases) and findings of Epstein-Barr virus DNA and HIV RNA in lung tissue of LIP patients. According to this theory, LIP is an extreme manifestation of the normal ability of lymphoid tissue in the lung to respond to inhaled and circulating antigens.

Symptoms and Signs

In adults, LIP causes symptoms of progressive dyspnea and cough. These manifestations progress over months or, in some cases, years and appear at a mean age of 54. Weight loss, fever, arthralgias, and night sweats occur but are less common.

In children, LIP causes bronchospasm, cough, or respiratory distress and failure to thrive, usually at age 2 or 3 yr.

Examination may reveal crackles. Findings such as hepatosplenomegaly, arthritis, and lymphadenopathy are uncommon and suggest an accompanying or alternative diagnosis.

Diagnosis

• High-resolution CT (HRCT)

• Pulmonary function tests

• For confirmation, biopsy (or sometimes serum protein abnormality in children)

Diagnosis is usually suspected in at-risk patients with compatible symptoms. Imaging tests, pulmonary function tests, and sometimes lung biopsy are done.

Chest x-ray shows bibasilar linear reticular or nodular opacities, a nonspecific finding that is present in a

number of pulmonary infections. Alveolar opacities, cystic dilatation of peripheral alveoli (honeycombing), or both may be present in more advanced disease. HRCT of the chest is done and helps establish the extent of disease, define the hilar anatomy, and identify pleural involvement. The HRCT findings of LIP are variable; however, their lymphatic distribution, along the peribronchovascular interstitium, interlobular septa, and presence within the visceral pleura distinguish LIP from usual interstitial pneumonia. Characteristic findings are centrilobular and subpleural nodules, thickened bronchovascular bundles, ground-glass opacities, and, rarely, diffuse cystic structures.

Pulmonary function tests show restrictive defects with reduced lung volumes and diffusing capacity for carbon monoxide (DLCO) and preserved airflow. Marked hypoxemia may occur. Bronchoalveolar lavage should be done to rule out infection and may reveal an increased number of lymphocytes.

About 80% of patients have a serum protein abnormality, most commonly a polyclonal gammopathy and, especially in children, hypogammaglobulinemia, the significance of which is unknown. These elements are sufficient to confirm the diagnosis in HIV-positive children. In adults, diagnosis requires lung biopsy with demonstration of expansion of the alveolar septae with lymphocytic and other immune cell (plasma cell, immunoblastic, and histiocytic) infiltrates. Infiltrates appear occasionally along bronchi and vessels but most commonly along alveolar septa. Immunohistochemical staining and flow cytometry must be done on the tissue to distinguish LIP from primary lymphomas. In LIP, the infiltrate is polyclonal (both T and B cells), whereas other lymphomas produce monoclonal infiltrates. Other common findings include germinal centers and multinucleated giant cells with noncaseating granulomas.

Prognosis

The natural history and prognosis of LIP are poorly understood. Good prognosis may correlate with more severe radiographic abnormalities, which may indicate a more vigorous immune response. Spontaneous resolution, resolution after treatment with corticosteroids or other immunosuppressive drugs, progression to lymphoma, or development of pulmonary fibrosis with respiratory insufficiency may ensue. Five-year survival is 50 to 66%. Common causes of death are infection, development of malignant lymphoma (5%), and progressive fibrosis.

Treatment

Treatment is with corticosteroids, cytotoxic drugs, or both, but, as with many other causes of interstitial lung diseases, the efficacy of this approach is unknown.

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis is accumulation of surfactant in alveoli. Etiology is almost always unknown. Symptoms are dyspnea, fatigue, and malaise. Diagnosis is based on bronchoalveolar lavage, although characteristic x-ray and laboratory test abnormalities occur. Treatment is with whole lung lavage. Five-year survival is about 80% with treatment.

Etiology

Pulmonary alveolar proteinosis is most often idiopathic and occurs in otherwise healthy men and women between 30 and 50 yr. Rare secondary forms occur in patients with acute silicosis, *Pneumocystis jirovecii* infection, hematologic cancers, or immunosuppression by drugs and in patients with significant inhalation exposures to aluminum, titanium, cement, and cellulose dusts. Rare congenital forms causing neonatal respiratory failure also exist. It is unclear whether idiopathic and secondary cases share a common pathophysiology.

Pathophysiology

Impaired alveolar macrophage processing of surfactant due to abnormal granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling is thought to contribute to the disorder, perhaps due to reduced or absent function of the common β chain of the GM-CSF/IL-13/IL-5 receptor on mononuclear cells (present in some children but not in adults with the disorder). Anti-GM-CSF antibodies have also been found in

most patients. Toxic lung injury is suspected but not proved in secondary inhalation causes.

Alveoli are filled with acellular lipoprotein surfactant that stains periodic acid-Schiff (PAS) positive. Alveolar and interstitial cells remain normal. Posterobasal lung segments are mostly affected. The pleura and mediastinum are unaffected.

Symptoms and Signs

Most patients present with progressive exertional dyspnea and weight loss, fatigue, malaise, or low-grade fever. Cough, occasionally producing chunky or gummy sputum, occurs but is less common. Clubbing and cyanosis are uncommon. Inspiratory crackles are rare because alveoli are fluid-filled; when crackles are present, they suggest infection.

Diagnosis

• Bronchoalveolar lavage

• Sometimes biopsy

Pulmonary alveolar proteinosis is usually first suspected when a chest x-ray is taken for nonspecific respiratory symptoms. The x-ray shows bilateral mid- and lower-lung field opacities in a butterfly distribution with normal hila.

Bronchoalveolar lavage is done. Lavage fluid is milky or opaque, stains PAS-positive, and is characterized by scattered surfactant-engorged macrophages, an increase in T lymphocytes, and high levels of surfactant apoprotein-A. Thoracoscopic or open lung biopsy is done when bronchoscopy is contraindicated or when specimens from lavage fluid are nondiagnostic. Tests typically done before treatment begins include high-resolution CT (HRCT), pulmonary function tests, ABGs, and laboratory tests.

HRCT shows ground-glass opacification, thickened intralobular structures, and interlobular septa in typical polygonal shapes (crazypaving). This finding is not specific, however, as it may also occur in patients with lipoid pneumonia, bronchoalveolar cell carcinoma, and *Pneumocystis jirovecii* pneumonia.

Pulmonary function tests show reduction in diffusing capacity for carbon monoxide (DLCO) that is disproportionate to the decreases in vital capacity, residual volume, functional residual capacity, and total lung capacity.

Laboratory test abnormalities include polycythemia, hypergammaglobulinemia, increased serum LDH levels, and increased serum surfactant proteins A and D. All abnormalities are suggestive but nondiagnostic. ABGs may show hypoxemia with mild to moderate exercise or at rest if disease is more severe.

Prognosis

Without treatment, pulmonary alveolar proteinosis remits spontaneously in up to 10% of patients. A single whole lung lavage is curative in up to 40%; other patients require lavage every 6 to 12 mo for many years. Five-year survival is about 80%; the most common cause of death is respiratory failure, typically occurring within the first year after diagnosis. Secondary pulmonary infections with bacteria (eg, *Mycobacteria*, *Nocardia*) and other organisms (*Aspergillus*, *Cryptococcus*, and other opportunistic fungi) occasionally develop because of impaired macrophage function; these infections require treatment.

Treatment

• Whole lung lavage

Treatment is unnecessary for patients without symptoms or for those with only mild symptoms. Whole lung lavage is done in patients with troubling dyspnea by using general anesthesia and a double-lumen

endotracheal tube. Lavage of one lung is done up to 15 times with 1 to 2 L saline while the other lung is ventilated. The process is then reversed. Lung transplantation is not done because the disorder recurs in the transplanted lung.

Systemic corticosteroids play no role in management and may increase the risk of secondary infection. The role of GM-CSF (IV or sc) in management remains to be determined. An open-label study showed clinical improvement in 57% of the patients studied.

Pulmonary Langerhans' Cell Histiocytosis

(Eosinophilic Granuloma; Pulmonary Granulomatosis X; Pulmonary Langerhans' Cell Granulomatosis; Histiocytosis X)

Pulmonary Langerhans' cell histiocytosis (PLCH) is proliferation of monoclonal Langerhans' cells in lung interstitium and airspaces. Etiology is unknown, but cigarette smoking plays a primary role. Symptoms are dyspnea, cough, fatigue, and pleuritic chest pain. Diagnosis is based on history and imaging tests and sometimes on bronchoalveolar lavage and biopsy findings. Treatment is smoking cessation. Corticosteroids are given in many cases, but efficacy is unknown. Lung transplantation is curative when combined with smoking cessation. Five-year survival is about 74%. Patients are at increased risk of cancer.

PLCH is a disease in which monoclonal CD1a-positive Langerhans' cells (a type of histiocyte) infiltrate the bronchioles and alveolar interstitium, accompanied by lymphocytes, plasma cells, neutrophils, and eosinophils. PLCH is one manifestation of Langerhans' cell histiocytosis (see p. 993), which can affect organs in isolation (most notably the lungs, skin, bones, pituitary, and lymph nodes) or simultaneously. PLCH occurs in isolation ≥ 85% of the time.

The etiology of PLCH is unknown, but the disease occurs almost exclusively in whites 20 to 40 yr of age who smoke. Men and women are affected equally. Women develop disease later, but any differences in disease presentation by sex may represent differences in smoking behavior. Pathophysiology may involve recruitment and proliferation of Langerhans' cells in response to cytokines and growth factors secreted by alveolar macrophages in response to cigarette smoke.

Symptoms and Signs

Typical symptoms and signs of PLCH are dyspnea, nonproductive cough, fatigue, fever, weight loss, and pleuritic chest pain, and 10 to 25% of patients have sudden, spontaneous pneumothorax. About 15% of patients are asymptomatic, with disease noted incidentally on a chest x-ray taken for another reason. Bone pain due to bone cysts (18%), rash (13%), and polyuria due to diabetes insipidus (5%) are the most common manifestations of extrapulmonary involvement and occur in up to 15% of patients, rarely being the presenting symptoms of PLCH. There are few signs of PLCH; the physical examination results are usually normal.

Diagnosis

• High-resolution CT (HRCT)

• Pulmonary function tests

• Sometimes bronchoscopy and biopsy

PLCH is suspected based on history and chest x-ray and is confirmed by HRCT and bronchoscopy with biopsy and bronchoalveolar lavage.

Chest x-ray classically shows bilaterally symmetric nodular opacities in the middle and upper lung fields with cystic changes and normal or increased lung volumes. The lung bases are often spared. Appearance may mimic COPD or lymphangioleiomyomatosis (see p. 1960). Confirmation on HRCT of middle and upper lobe cysts (often with bizarre shapes) and/or nodules with interstitial thickening is considered

diagnostic of PLCH. Pulmonary function test findings are normal, restrictive, obstructive, or mixed depending on when the test is done during the course of the disease. Most commonly, the diffusing capacity for carbon monoxide (DLCO) is reduced and exercise is impaired.

Bronchoscopy and biopsy are indicated when imaging and pulmonary function tests are inconclusive. Finding > 5% of CD1a cells in bronchoalveolar lavage fluid is highly suggestive of the disease. Biopsy shows proliferation of Langerhans' cells with occasional clustering of eosinophils (the origin of the outdated term eosinophilic granuloma) in the midst of cellular and fibrotic nodules that may take on a stellate configuration. Immunohistochemical staining is positive for CD1a, S-100 protein, and HLA-DR antigens.

Treatment

• Smoking cessation

• Possibly corticosteroids and cytotoxic drugs or lung transplantation

The main treatment is smoking cessation, which leads to symptom resolution in up to one third of patients. Empiric use of corticosteroids and cytotoxic drugs is common practice even though their effectiveness is unproved. Lung transplantation is an option for otherwise healthy patients with accelerating respiratory insufficiency, but the disorder may recur in the transplanted lung if the patient continues or resumes smoking.

Spontaneous resolution of symptoms occurs in some patients with minimally symptomatic disease; 5-yr survival is about 75%, and median survival is 12 yr. However, some patients develop slowly progressive disease, for which the clinical markers include continued smoking, age extremes, multiorgan involvement, persistent constitutional symptoms, numerous cysts on chest x-ray, reduced DLCO, low forced expiratory volume in 1 sec (FEV_1)/forced vital capacity (FVC) ratio (< 66%), high residual volume (RV)/total lung capacity (TLC) ratio (> 33%), and need for prolonged corticosteroid use. Cause of death is respiratory insufficiency or cancer. Lung cancer risk is increased because of cigarette smoking.

Chapter 200. Sarcoidosis

Introduction

Sarcoidosis is a disorder resulting in noncaseating granulomas in one or more organs and tissues; etiology is unknown. The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ. Pulmonary symptoms range from none (limited disease) to exertional dyspnea and, rarely, lung or other organ failure (advanced disease). Diagnosis usually is first suspected because of pulmonary involvement and is confirmed by chest x-ray, biopsy, and exclusion of other causes of granulomatous inflammation. First-line treatment is corticosteroids. Prognosis is excellent for limited disease but poor for more advanced disease.

Sarcoidosis affects mostly people aged 20 to 40 but occasionally affects children and older adults. Worldwide, prevalence is greatest in black Americans and northern Europeans, especially Scandinavians. Disease presentation varies widely by racial and ethnic background, with black Americans and Puerto Ricans having more frequent extrathoracic manifestations. Sarcoidosis is slightly more prevalent in women. The incidence increases in winter and early spring for unknown reasons.

Lofgren's syndrome: Lofgren's syndrome is a type of acute sarcoidosis that manifests as a triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It has distinct features, including fever, malaise, joint disease, and sometimes uveitis and parotitis. It is more common among Scandinavian and Irish women.

Lofgren's syndrome is often self-limited. Patients usually respond to NSAIDs. Rate of relapse is low.

Etiology

Sarcoidosis is thought to be due to an inflammatory response to environmental exposure in a genetically susceptible person. Proposed triggers include

- Viral, bacterial, and mycobacterial infections
- Inhalation of various agents: inorganic (eg, aluminum, zirconium, talc) or organic (eg, pine tree pollen, clay)

Pathophysiology

The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T lymphocytes and macrophages, release of cytokines and chemokines, and organization of responding cells into granulomas. Clusters of disease in families and communities suggest a genetic predisposition, shared exposures, or, less likely, person-to-person transmission.

The result of the inflammatory process is formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis. Granulomas are collections of mononuclear cells and macrophages that are differentiated into epithelioid and multinucleated giant cells, surrounded by lymphocytes, plasma cells, mast cells, fibroblasts, and collagen. Granulomas occur most commonly in the lungs and lymph nodes but can involve the liver, spleen, eyes (see p. 609), sinuses, skin, bones, joints, skeletal muscle, kidneys, reproductive organs, heart, salivary glands, and nervous system. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions.

Symptoms and Signs

Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness. Accordingly, frequent reassessment for new symptoms in different organs is needed. Most cases are probably asymptomatic and thus go undetected. Pulmonary disease occurs in > 90% of adult patients.

Symptoms and signs may include dyspnea, cough, chest discomfort, and crackles. Fatigue, malaise,

weakness, anorexia, weight loss, and low-grade fever are also common; sarcoidosis is an unusual cause of fever of unknown origin. Nontender lymphadenopathy is often the only sign. Systemic involvement causes various symptoms (see Table 200-1), which vary by race, sex, and age. Blacks are more likely than whites to have involvement of the eye, liver, bone marrow, peripheral lymph nodes, and skin; erythema nodosum is an exception. Women are more likely to have erythema nodosum and eye or nervous system involvement. Men and older patients are more likely to be hypercalcemic.

In children < 4 yr, arthritis, rash, and uveitis are the most common manifestations. Sarcoidosis may be confused with juvenile RA in this age group.

Diagnosis

• Chest imaging

• Biopsy

• Exclusion of other granulomatous disorders

[**Table 200-1.** Systemic Involvement in Sarcoidosis]

Sarcoidosis is most often suspected when hilar adenopathy is incidentally detected on chest x-ray. These changes are the most common abnormality, and the x-ray appearance is roughly predictive of the likelihood of spontaneous remission (see Table 200-2) in patients with pulmonary involvement. Therefore, if sarcoidosis is suspected, a chest x-ray should be the first test if it has not already been done.

A normal chest x-ray generally excludes the diagnosis; however, high-resolution CT may be indicated if sarcoidosis is strongly suspected because CT is more sensitive for detecting hilar and mediastinal lymphadenopathy. CT findings in more advanced stages (II to IV) include thickening of the bronchovascular bundles and bronchial walls; beading of the interlobular septa; ground-glass opacification; parenchymal nodules, cysts, or cavities; and traction bronchiectasis.

When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on biopsy and exclusion of alternative causes of granulomatous disease (see Table 200-3).

[**Table 200-2.** Staging Sarcoidosis]

The diagnostic evaluation, therefore, requires the following:

• Selection of a biopsy site

• Exclusion of other causes of granulomatous disease

• Assessment of the severity and extent of disease to determine whether therapy is indicated

Sites for biopsy: Appropriate biopsy sites may be obvious from physical examination and initial assessment; peripheral lymph nodes, skin lesions, and conjunctivae are all easily accessible. However, bronchoscopic transbronchial biopsy is the diagnostic procedure of choice in patients with intrathoracic involvement because sensitivity is as high as 90% when an experienced clinician does the procedure. Video-assisted thoracoscopy can provide access to lung tissue when bronchoscopic transbronchial biopsy is nondiagnostic. Mediastinoscopy is sometimes done when hilar or mediastinal lymphadenopathy exists in the absence of pulmonary infiltrates, especially if lymphoma is in the differential diagnosis. However, even in patients with only mediastinal adenopathy on x-ray or CT, transbronchial biopsies are often diagnostic. Open lung biopsy provides another way to obtain tissue but requires general anesthesia and is now rarely necessary. Clinical and x-ray findings may be accurate enough for diagnosis in stage I disease or in stage II disease when biopsy is not possible.

Exclusion of other diagnoses: Exclusion of other diagnoses is critical, especially when symptoms and x-ray signs are minimal, because many other disorders and processes can cause granulomatous inflammation (see Table 200-3). Biopsy tissue should be cultured for fungi and mycobacteria. Exposure history to occupational (silicates, beryllium), environmental (moldy hay, birds, and other antigenic triggers of hypersensitivity pneumonitis), and infectious (TB, coccidioidomycosis, histoplasmosis) antigens should be explored. PPD skin testing should be done early in the assessment along with anergy controls.

Disease severity assessment: Severity is assessed with

• Pulmonary function tests

• Exercise pulse oximetry

Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DLCO) in advanced disease. Airflow obstruction also occurs and may suggest involvement of the bronchial mucosae. Pulse oximetry is often normal when measured

[**Table 200-3.** Differential Diagnosis of Sarcoidosis]

at rest but may show effort desaturation with more extensive lung involvement. ABG analysis at rest and during exercise is more sensitive than pulse oximetry.

Recommended screening tests for extrapulmonary disease include

• ECG

• Slit-lamp ophthalmologic examination

• Routine blood tests to evaluate renal and hepatic function

• Serum Ca levels

Echocardiography, neuroimaging, lumbar puncture, bone x-rays or MRI, and electromyography may be appropriate when symptoms suggest cardiac, neurologic, or rheumatologic disorders. Abdominal CT with radiopaque dye is not routinely recommended but can provide evidence of hepatic or splenic involvement (eg, enlargement, hypolucent lesions).

Laboratory testing plays an adjunctive role in establishing the diagnosis and extent of organ involvement. CBC may show anemia, eosinophilia, or leukopenia. Serum Ca may be elevated because vitamin D analogs are produced by activated macrophages. BUN, creatinine, and liver function test results may be elevated in renal and hepatic sarcoidosis. Total protein may be elevated because of hypergammaglobulinemia. Elevated ESR is common but nonspecific. Measurement of Ca in a urine specimen collected over 24 h is recommended to exclude hypercalciuria, even in patients with normal serum Ca levels. Elevated serum ACE levels also suggest sarcoidosis but are nonspecific and may be low in patients taking ACE inhibitors or elevated in patients with various other conditions (eg, hyperthyroidism, Gaucher's disease, silicosis, mycobacterial disease, hypersensitivity pneumonitis). However, ACE levels may be useful for monitoring disease activity and therapeutic response in patients with confirmed sarcoidosis. Increased ACE levels in CSF may be useful for diagnosing CNS sarcoidosis.

Other adjunctive tests include bronchoalveolar lavage (BAL) and gallium scanning. BAL is used to help exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes > 10%), a CD4+/CD8+ ratio of > 3.5 in the lavage fluid cell differential, or both suggest the diagnosis in the proper clinical context. However, absence of these findings does not exclude sarcoidosis.

Whole-body gallium scanning may provide useful supportive evidence in the absence of tissue confirmation. Symmetric increased uptake in mediastinal and hilar nodes (lambda sign) and in lacrimal,

parotid, and salivary glands (panda sign) are patterns highly suggestive of sarcoidosis. A negative result in patients taking prednisone is unreliable.

Prognosis

Although spontaneous improvement is common, the manifestations of the disorder and its severity are highly variable, and many patients require corticosteroids some time during the course of their disease. Thus, serial monitoring for evidence of relapse is imperative. In about 90% of patients who have spontaneous remission, remission occurs within the first 2 yr after diagnosis; < 10% of these patients have relapses after 2 yr. Patients who do not experience remission within 2 yr are likely to have chronic disease.

Sarcoidosis is thought to be chronic in up to 30% of patients, and 10 to 20% experience permanent sequelae. The disease is fatal in 1 to 5% of patients, typically due to respiratory failure caused by pulmonary fibrosis, and less often due to pulmonary hemorrhage caused by aspergilloma. However, in Japan, infiltrative cardiomyopathy causing heart failure and arrhythmias is the most common cause of death.

Prognosis is worse for patients with extrapulmonary sarcoidosis and for blacks. Recovery occurs in 89% of whites and 76% of blacks with no extrathoracic disease and in 70% of whites and 46% of blacks with extrathoracic disease.

Good prognostic signs include

• Erythema nodosum

• Acute arthritis

Poor prognostic signs include

• Uveitis

• Lupus pernio

• Chronic hypercalcemia

• Neurosarcoidosis

• Nephrocalcinosis

• Myocardial disease

• Extensive pulmonary involvement

Little difference is demonstrable in long-term outcome between treated and untreated patients, and relapse is common when treatment ends.

Treatment

• Sometimes corticosteroids

• Rarely immunosuppressants

Because sarcoidosis often spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial x-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (eg, routine renal and liver function testing). Patients who require treatment regardless of stage include those with the following:

- Worsening symptoms
- Limitation of activity
- Markedly abnormal or deteriorating lung function
- Worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension)
- Heart, nervous system, or eye involvement
- Renal or hepatic insufficiency or failure
- Disfiguring skin or joint disease

Treatment is with corticosteroids. A standard protocol is prednisone 0.3 to 1 mg/kg po once/day depending on symptoms and severity of findings. Alternate-day regimens are also used: eg, prednisone 40 to 60 mg po once every other day. Although patients rarely require > 40 mg/day, higher doses may be needed to reduce complications in patients with ocular, myocardial, or neurologic disease. Response usually occurs within 2 to 4 wk, so symptoms and results of chest x-ray and pulmonary function tests may be reassessed between 4 and 12 wk. Chronic, insidious cases may respond more slowly. Corticosteroids are tapered to a maintenance dose (eg, prednisone ≤ 10 mg every other day if possible) after evidence of response and are continued for a minimum of 12 mo if improvement occurs. The optimal duration of treatment is unknown. Premature taper can result in relapse. The drug is slowly stopped if response is absent or equivocal. Corticosteroids can ultimately be stopped in most patients, but because relapse occurs up to 50% of the time, monitoring should be repeated, usually every 3 to 6 mo. Corticosteroid treatment should be resumed for recurrence of symptoms and signs, including dyspnea, arthralgia, fever, hepatic insufficiency, cardiac arrhythmia, CNS involvement, hypercalcemia, ocular disease uncontrolled by local drugs, and disfiguring skin lesions.

Data on use of inhaled corticosteroids for pulmonary sarcoidosis are not definitive, but some evidence suggests that this route of administration can relieve cough in patients with endobronchial involvement. Topical corticosteroids may be useful in some cases of dermatologic and ocular disease.

About 10% of patients requiring therapy are unresponsive to tolerable doses of a corticosteroid and should be given a 6-mo trial of methotrexate starting at 2.5 mg po once/wk and increasing in increments of 2.5 mg/wk to a total of 10 to 15 mg/wk as tolerated to keep the WBC count > 3000/μL. Initially, methotrexate and corticosteroids are both given; over 8 wk, the corticosteroid dose can be tapered and, in many cases, stopped. The maximal response to methotrexate, however, may take 6 to 12 mo. In such cases, prednisone must be tapered more slowly. Serial blood counts and liver enzyme tests should be done every 1 to 2 wk initially and then every 4 to 6 wk once a stable dose is achieved. Foliate (1 mg po once/day) is recommended for patients treated with methotrexate.

Other drugs reported to be effective in small numbers of patients who are corticosteroid-resistant or who experience complicating adverse effects include azathioprine, cyclophosphamide, chlorambucil, chloroquine or hydroxychloroquine, thalidomide, pentoxifylline, and infliximab.

Hydroxychloroquine 200 mg po bid to tid can be as effective as corticosteroids for treating hypercalcemia or disfiguring skin sarcoidosis. Although immunosuppressants are often more effective in refractory cases, relapse is common after cessation.

No available drugs have consistently prevented pulmonary fibrosis.

Lung transplantation is an option for patients with end-stage pulmonary involvement, although disease may recur in the transplanted organ.

Chapter 201. Environmental Pulmonary Diseases

Introduction

Environmental pulmonary diseases result from inhalation of dusts, allergens, chemicals, gases, and environmental pollutants. The lungs are continually exposed to the external environment and are susceptible to a host of environmental diseases. Pathologic processes can involve any part of the lungs, including the airways (eg, in occupational asthma, reactive airways dysfunction syndrome, or toxic inhalations), interstitium (eg, or pneumoconioses in hypersensitivity pneumonitis), and pleura (eg, in asbestos-related diseases).

Prevention of occupational and environmental pulmonary diseases centers on reducing exposure (primary prevention). Exposure can be limited by the use of

• Administrative controls (eg, limiting the number of people exposed to hazardous conditions)

• Engineering controls (eg, enclosures, ventilation systems, safe clean-up procedures)

• Product substitution (eg, using safer, less toxic materials)

• Respiratory protection devices (eg, respirator, dust mask, gas mask)

Many clinicians erroneously assume that a patient who has used a respirator or another respiratory protection device has been well protected. Although respirators do afford a degree of protection, especially when fresh air is provided by tank or air hose, the benefit is limited and idiosyncratic. When recommending use of a respirator, clinicians should consider several factors. Workers with cardiovascular disease may be unable to carry out jobs that require strenuous work, especially if they must wear a self-contained breathing apparatus (tank). Respirators that are tight-fitting and that require the wearer to draw air through filter cartridges can increase the work of breathing, which can be especially difficult for patients with asthma, COPD, or interstitial lung diseases.

Medical surveillance is a form of secondary prevention. Workers can be offered medical tests that identify disorders early when treatment might help reduce long-term consequences.

Air Pollution-Related Illness

The major components of air pollution in developed countries are nitrogen dioxide (from combustion of fossil fuels), ozone (from the effect of sunlight on nitrogen dioxide and hydrocarbons), and suspended solid or liquid particles. Indoors, passive smoking is an additional source, as is burning of biomass fuel in developing countries (eg, for cooking and heating).

High levels of air pollution can adversely affect lung function and trigger asthma and COPD exacerbations. People living in areas with high traffic, especially when stagnant air is created by thermal inversions, are at particular risk. All of the so-called criteria air pollutants (oxides of nitrogen, oxides of sulfur, ozone, carbon monoxide, lead, particulates), except carbon monoxide and lead, cause airway hyperreactivity. Long-term exposure may increase respiratory infections and symptoms in the general population, especially in children.

Ozone, which is the major component of smog, is a strong respiratory irritant and oxidant. Ozone levels tend to be highest in the summer and in the late morning and early afternoon. Short-term exposures can cause dyspnea, chest pain, and airways reactivity. Children who regularly participate in outdoor sports during days on which ozone pollution is high are more likely to develop asthma. Long-term exposure to ozone produces a small, permanent decrease in lung function.

Oxides of sulfur, resulting from combustion of fossil fuels that are high in sulfur content, can create acid aerosols with high solubility, which are likely to be deposited in the upper airways. Sulfur oxides can induce airway inflammation, possibly increasing the risk of chronic bronchitis as well as inducing bronchoconstriction.

Particulate air pollution is a complex mixture, derived from fossil fuel combustion (especially diesel). The particles can have both local and systemic inflammatory effects, suggesting an explanation for their impact on both pulmonary and cardiovascular health. So-called PM2.5 (particulate matter < 2.5 µm diameter) produce a greater inflammatory response per mass than do larger particles. Data suggest that particulate air pollution increases death rates from all causes, especially cardiovascular and respiratory illness.

Air pollution data have raised concerns regarding the potential health effects of even smaller particles, so-called nanoparticles, but clinical evidence of disorders related to exposure to nanoparticles has yet to be reported.

Asbestos-Related Disorders

Asbestos-related disorders are caused by inhalation of asbestos fibers. The disorders include asbestosis, lung carcinoma, nonmalignant pleural plaque formation and thickening, benign pleural effusions, and mesothelioma. Asbestosis and mesothelioma both cause progressive dyspnea, as do extensive effusions and plaques. Diagnosis is based on history and chest x-ray or CT findings and, in the case of cancer, tissue biopsy. Treatment is supportive, except for cancer, which may require surgery, chemotherapy, or both.

Asbestos is a family of naturally occurring silicates whose heat-resistant and structural properties made it useful for inclusion in construction and shipbuilding materials, automobile brakes, and some textiles. Chrysotile (a serpentine fiber), crocidolite, and amosite (amphibole, or straight fibers) are the 3 main types of asbestos that cause disease. Asbestos can affect the lung, the pleura, or both.

Asbestosis

Asbestosis is a form of interstitial pulmonary fibrosis caused by asbestos exposure.

Asbestosis is a much more common consequence of asbestos exposure than cancer. Shipbuilders, textile and construction workers, home remodelers, workers who do asbestos abatement, and miners who are exposed to asbestos fibers are among the many workers at risk. Secondhand exposure may occur among family members of exposed workers and among people who live close to mines.

Pathophysiology

Alveolar macrophages attempting to engulf inhaled fibers release cytokines and growth factors that stimulate inflammation, oxidative injury, collagen deposition, and ultimately fibrosis. Asbestos fibers may also be directly toxic to lung tissue. Risk of disease is generally related to duration and intensity of exposure and type, length, and thickness of inhaled fibers.

Symptoms and Signs

Asbestosis is initially asymptomatic but can cause progressive dyspnea, nonproductive cough, and fatigue. The disorder progresses in > 10% of patients even after cessation of exposure. Advanced asbestosis may cause clubbing, dry bibasilar crackles, and, in severe cases, symptoms and signs of right ventricular failure (cor pulmonale).

Diagnosis

• Chest x-ray, preferably chest CT

• Pulmonary function tests

• Sometimes bronchoalveolar lavage or lung biopsy

Diagnosis is based on history of exposure and chest x-ray or chest CT. Chest x-ray shows linear reticular

opacities signifying fibrosis, usually in the peripheral lower lobes. Opacities are often bilateral and are often accompanied by pleural changes (see p. 1974). Honeycombing signifies more advanced disease, which may involve the mid and lower lung fields. As with silicosis, severity is graded on the International Labor Organization scale (International Classification of Radiographs of Pneumoconioses) based on size, shape, location, and profusion of opacities. In contrast to silicosis, asbestosis produces reticular opacities with a lower lobe predominance. Hilar and mediastinal adenopathy and nodular opacities are uncharacteristic and suggest a different diagnosis. Chest x-ray is insensitive; thin-section chest CT is useful when asbestosis is a likely diagnosis. CT is also superior to chest x-ray in identifying pleural abnormalities.

Pulmonary function tests, which may show reduced lung volumes and diffusing capacity for carbon monoxide (DLCO), are nonspecific but help characterize changes in lung function over time. Pulse oximetry measured at rest and with exertion is nonspecific but sensitive for detecting asbestos-induced impairment.

Bronchoalveolar lavage or lung biopsy is indicated only when noninvasive measures fail to provide conclusive diagnosis; demonstration of asbestos fibers indicates asbestosis in people with pulmonary fibrosis, although such fibers can occasionally be found in lungs of exposed people without disease and may not be present in specimens from patients with asbestosis. Thus, demonstration of asbestos fibers may be helpful but is not necessary for diagnosis.

Prognosis

Prognosis varies; many patients have no or mild symptoms and do well, whereas some develop progressive dyspnea and a few develop respiratory failure, right ventricular failure, and cancer.

Lung cancer (usually non-small cell lung carcinoma) develops in patients with asbestosis at 8 to 10 times the rate of those without asbestosis and is especially common among workers exposed to amphibole fibers, although all forms of inhaled asbestos have been associated with an elevated cancer risk. Asbestos and smoking have a synergistic effect on lung cancer risk (see p. 2005).

Treatment

• Supportive care

No specific treatment exists. Early detection of hypoxemia and right ventricular failure leads to use of supplemental O_2 and treatment of heart failure. Pulmonary rehabilitation can be helpful for patients with impairment.

Prevention

Preventive measures include eliminating exposure, asbestos abatement in occupational and nonoccupational settings, smoking cessation, and pneumococcal and influenza vaccination. Smoking cessation is particularly important in light of the multiplicative risk of lung cancer in patients who have both tobacco smoke and asbestos exposures.

Mesothelioma

Pleural mesothelioma is the only known pleural cancer and is caused by asbestos exposure in nearly all cases.

Asbestos workers have up to a 10% lifetime risk of developing the disorder, with an average latency of 30 yr. Risk is independent of smoking. Mesothelioma can spread locally, or it can metastasize to the hilar and mediastinal lymph nodes, pericardium, diaphragm, peritoneum, liver, adrenals, or kidneys and, rarely, the tunica vaginalis of the testis.

Symptoms and Signs

Patients most often present with dyspnea and nonpleuritic chest pain. Constitutional symptoms are uncommon at presentation. Invasion of the chest wall and other adjacent structures may cause severe pain, hoarseness, dysphagia, Horner's syndrome, brachial plexopathy, or ascites.

Diagnosis

• Chest x-ray

• Pleural fluid cytology or pleural biopsy

• Sometimes video-assisted thorascopic surgery (VATS) or thoracotomy

• Staging with chest CT, mediastinoscopy, and MRI or sometimes with PET and bronchoscopy

The pleural form of mesothelioma, which represents > 90% of all cases (the other 10% include pericardial and peritoneal mesotheliomas), appears on x-ray as diffuse unilateral or bilateral pleural thickening that appears to encase the lungs, usually producing blunting of the costophrenic angles. Pleural effusions are present in 95% of cases and are typically unilateral, large, and hemorrhagic. Diagnosis is based on pleural fluid cytology or pleural biopsy. If diagnosis is uncertain after these procedures, biopsy by VATS or thoracotomy is done.

Staging is done with chest CT, mediastinoscopy, and MRI. Sensitivity and specificity of MRI and CT are comparable, although MRI is helpful in determining tumor extension into the spine or spinal cord. PET may have better sensitivity and specificity for distinguishing benign from malignant pleural thickening. Bronchoscopy should be done to exclude coexisting endobronchial lung cancers. Increased levels of hyaluronidase in pleural fluid are suggestive but not diagnostic of mesothelioma. Soluble mesothelin-related proteins released into the serum by mesothelial cells are being studied as possible tumor markers for disease detection and monitoring, but the false-positive rate may limit their effectiveness.

Prognosis

Mesothelioma remains an incurable cancer, and long-term survival is uncommon. Surgery to remove the pleura, ipsilateral lung, phrenic nerve, hemidiaphragm, and pericardium combined with chemotherapy or radiation therapy may be considered, although it does not substantially change prognosis or survival time. No treatment substantially prolongs survival. Survival from time of diagnosis averages 8 to 15 mo, depending on the location and cell type. A few patients, usually younger patients with shorter duration of symptoms, have a more favorable prognosis, sometimes surviving for several years after diagnosis.

Treatment

• Supportive care

• Pleurodesis or pleurectomy for pleural effusions and relief of dyspnea

• Analgesia with opioids and sometimes radiation therapy

• Chemotherapy for tumor shrinkage and symptom relief

• Experimental therapies

Complete surgical resection usually is not feasible. Combination pemetrexed (an antifolate antimetabolite) and cisplatin shows promise but warrants further study.

The major focus of treatment is supportive care and relief of pain and dyspnea. Given the diffuse nature of the disorder, radiation therapy is usually unsuitable except to treat localized pain or needle-tract metastases. It is not generally used for treatment of nerve root pain. Pleurodesis or pleurectomy can be used to help reduce dyspnea caused by pleural effusions. Adequate analgesia is important but difficult to

achieve. Usually, opioids, both transdermal and delivered via indwelling epidural catheters, are used. Chemotherapy using cisplatin and gemcitabine relieves symptoms in most cases and sometimes decreases tumor size. Multimodality therapies are advocated by some authorities. Intrapleural injection of granulocyte-macrophage colony-stimulating factor or interferon-γ1b, IV ranpirnase (a ribonuclease), and gene therapies are under study.

Other Asbestos-Related Pleural Disease

Pleural disease, a hallmark of asbestos exposure, includes formation of pleural plaques, calcification, thickening, rounded atelectasis, adhesions, effusion, and mesothelioma (see p. 1973).

Pleural disease causes effusion but few symptoms. All pleural changes are diagnosed by chest x-ray or CT, though chest CT is more sensitive than chest x-ray for detecting pleural disorders. Treatment is rarely needed except for cancer.

Discrete plaques, which occur in up to 60% of workers exposed to asbestos, typically affect the bilateral parietal pleurae between the 5th and 9th ribs and adjacent to the diaphragm. Plaque calcification is common and can lead to misdiagnosis of severe pulmonary disease when radiographically superimposed on lung fields. CT can distinguish pleural from parenchymal disease in this setting. Fat stripes may be mistaken for pleural plaques on chest x-ray. CT can distinguish pleural disease from fat.

Diffuse thickening affects visceral as well as parietal pleurae. It may be an extension of pulmonary fibrosis from parenchyma to the pleurae or a nonspecific reaction to pleural effusion. With or without calcification, pleural thickening can cause a restrictive defect.

Rounded atelectasis is a benign manifestation of pleural thickening in which invagination of pleura into the parenchyma can entrap lung tissue, causing atelectasis. On chest x-ray and CT, it typically appears as a curvilinear cicatricial mass, often in the lower lung zones, and can be confused with a pulmonary cancer.

Pleural effusions occur but are less common than the other pleural changes they accompany. These benign effusions are usually bilateral, exudative, and often hemorrhagic. They typically resolve spontaneously (see p. 1995).

Beryllium Disease

(Berylliosis)

Acute beryllium disease and chronic beryllium disease are caused by inhalation of dust or fumes from beryllium compounds and products. Acute beryllium disease is now rare; chronic beryllium disease is characterized by formation of granulomas throughout the body, especially in the lungs, intrathoracic lymph nodes, and skin. Chronic beryllium disease causes progressive dyspnea, cough, and fatigue. Diagnosis is by history, beryllium lymphocyte proliferation test, and biopsy. Treatment is with corticosteroids.

Etiology

Beryllium exposure is a common but under-recognized cause of illness in many industries, including beryllium mining and extraction, alloy production, metal alloy machining, electronics, telecommunications, nuclear weapon manufacture, defense, aircraft, automotive, aerospace, and metal scrap, computer, and electronics recycling. Because small amounts of beryllium are toxic and are added to many copper, aluminum, nickel, and magnesium alloys, workers are often unaware of their exposure and its risks.

Pathophysiology

Acute beryllium disease is a chemical pneumonitis causing diffuse parenchymal inflammatory infiltrates and nonspecific intra-alveolar edema. Other tissues (eg, skin and conjunctivae) may be affected. Acute

beryllium disease is now rare because most industries have reduced exposure levels, but cases were common between 1940 and 1970, and many cases progressed from acute to chronic beryllium disease.

Chronic beryllium disease remains a common illness in industries that use beryllium and beryllium alloy. It differs from most pneumoconioses in that it is a cell-mediated hypersensitivity disease. Beryllium is presented to CD4+ T lymphocytes by antigen-presenting cells, principally in HLA-DP molecules. T lymphocytes in the blood, lungs, or other organs, in turn, recognize the beryllium, proliferate, and form T-lymphocyte clones. These clones then release proinflammatory cytokines, such as tumor necrosis factor-α, IL-2, and interferon-γ. These cytokines amplify the immune response, resulting in formation of mononuclear cell infiltrates and noncaseating granulomas in target organs where beryllium has deposited. On average, about 2% to 6% of beryllium-exposed people develop beryllium sensitization (defined by positive blood lymphocyte proliferation to beryllium salts in vitro), with most progressing to disease. In certain high-risk groups, such as beryllium metal and alloy machinists, chronic beryllium disease prevalence is > 17%. Workers with bystander exposures, such as secretaries and security guards, also develop sensitization and disease but at lower rates. The typical pathologic consequence is a diffuse pulmonary, hilar, and mediastinal lymph node granulomatous reaction that is histologically indistinguishable from sarcoidosis. Early granuloma formation with mononuclear and giant cells can also occur. Many lymphocytes are found when cells are washed from the lungs (bronchoalveolar lavage [BAL]) during bronchoscopy. These T lymphocytes proliferate when exposed to beryllium in vitro, much as the blood cells do (a test called beryllium lymphocyte proliferation test [BeLPT]).

Symptoms and Signs

Patients with chronic beryllium disease often have dyspnea, cough, weight loss, and a variable chest x-ray pattern, typically showing nodular opacities in the mid and upper lung zones, frequently with hilar and mediastinal adenopathy. Patients complain of insidious and progressive exertional dyspnea, cough, chest pain, weight loss, night sweats, and fatigue. Symptoms may develop within months of first exposure or > 40 yr after exposure has ceased. Some people remain asymptomatic.

Diagnosis

• Beryllium lymphocyte proliferation test (using blood or bronchoalveolar lavage cells)

• Chest x-ray or CT

Diagnosis depends on a history of exposure, the appropriate clinical manifestations, and an abnormal blood or BAL BeLPT or both. BAL BeLPT is highly sensitive and specific, helping to distinguish chronic beryllium disease from sarcoidosis and other forms of diffuse pulmonary disease. Chest x-ray may be normal or show diffuse infiltrates that can be nodular, reticular, or have a hazy ground-glass appearance, often with hilar adenopathy resembling the pattern seen in sarcoidosis. A miliary pattern also occurs. High-resolution CT is more sensitive than x-ray, although cases of biopsy-proven disease occur even in people with normal imaging tests.

Prognosis

Acute beryllium disease can be fatal, but prognosis is usually excellent unless progression to chronic beryllium disease occurs. Chronic beryllium disease often results in progressive loss of respiratory function. Early abnormalities include air flow obstruction and decreased oxygenation on ABG at rest and during exercise testing. Decreased diffusing capacity for carbon monoxide (DLCO) and restriction appear later. Pulmonary hypertension and right venticular failure develop in about 10% of cases, with death due to cor pulmonale. Beryllium sensitization progresses to chronic beryllium disease at a rate of about 6%/yr after initial detection through workplace medical surveillance programs. Subcutaneous granulomatous nodules caused by inoculation with beryllium splinters or dust usually persist until excised.

Treatment

• Corticosteroids

- In acute beryllium disease, sometimes mechanical ventilation
- In chronic beryllium disease, sometimes supplemental O_2, pulmonary rehabilitation, and treatment for right ventricular failure
- In end-stage chronic beryllium disease, sometimes lung transplantation

In acute disease, the lungs often become edematous and hemorrhagic. Mechanical ventilation is necessary in severely affected patients.

Some patients with chronic beryllium disease never require treatment because the disease progresses relatively slowly. When needed, treatment is with corticosteroids, which decrease symptoms and improve oxygenation. Treatment is generally started only in patients with significant symptoms and evidence of abnormal gas exchange or evidence of an accelerated decline in lung function or oxygenation. In symptomatic patients with abnormal pulmonary function, prednisone 40 to 60 mg po once/day or every other day is given for 3 to 6 mo. Then, measures of pulmonary physiology and gas exchange are repeated to document a response to therapy, and the dose is gradually tapered to the lowest dose that maintains symptomatic and objective improvement (usually about 10 to 15 mg once/day or every other day). Lifelong treatment with corticosteroids is usually required. There is anecdotal evidence that the addition of methotrexate (10 to 25 mg po once/wk) reduces the need for corticosteroids as it does in sarcoidosis.

Spontaneous remission of chronic beryllium disease is rare. In patients with end-stage disease, lung transplantation can be lifesaving. Other supportive measures, such as supplemental O_2 therapy, pulmonary rehabilitation, and drugs for treatment of right ventricular failure, are used as needed.

Prevention

Industrial dust suppression is the basis for preventing beryllium exposure. Exposures must be reduced to levels that are as low as reasonably achievable—preferably more than 50-fold below current Occupational Safety and Health Administration (OSHA) standards—to reduce the risk of sensitization and chronic beryllium disease. Medical surveillance, using blood BeLPT and chest x-ray, is recommended for all exposed workers, including those with indirect contact. Both acute and chronic disease must be promptly recognized and affected workers removed from further beryllium exposure.

Building-Related Illnesses

Building-related illnesses (BRIs) are a heterogeneous group of disorders whose etiology is linked to the environment of modern airtight buildings. Such buildings are characterized by sealed windows and dependence on heating, ventilation, and air conditioning systems for circulation of air. Most cases occur in nonindustrial office buildings, but cases can occur in apartment buildings, single-family homes, schools, museums, and libraries.

BRIs can be specific or nonspecific.

Specific BRIs: Specific BRIs are those for which a link between building-related exposure and illness is proved. Examples include

- *Legionella* infection (see p. 1253)
- Occupational asthma (see p. 1979)
- Hypersensitivity pneumonitis (see p. 1956)
- Inhalational fever

Inhalational fever is a febrile reaction caused by exposure to organic aerosols or dusts. Names used to describe this type of BRI include humidifier fever, grain fever, swine confinement fever, and mycotoxicosis,

depending on the causative agent. Metal fumes and polymer fumes can also cause febrile illness. The term organic dust toxic syndrome (ODTS) has been used to encompass the subacute febrile and respiratory reaction to organic dust that is typically highly contaminated with bacterial endotoxin. Toxic pneumonitis is a commonly used but less specific term.

Humidifier fever occurs in nonindustrial buildings as a consequence of humidifiers or other types of ventilation units serving as a reservoir for the growth of bacteria or fungi and as a method of aerosolizing these contaminants. The disorder usually manifests as low-grade fever, malaise, cough, and dyspnea. Improvement after removal from exposure (eg, weekend away from the office building) is often one of the first indications of etiology. Humidifier fever has an acute onset and is self-limiting (usually 2 to 3 days). Physical signs may be absent or subtle. Clusters of cases are common.

Unlike immunologically mediated conditions (eg, hypersensitivity pneumonitis, building-related asthma), inhalational fevers do not require a period of sensitization. The disorder can occur after initial exposure. Acute episodes do not generally require treatment apart from antipyretics and removal from the contaminated environment. If symptoms persist, evaluation may be required to rule out infection, hypersensitivity pneumonitis, or other conditions. Biologic sampling to detect airborne microbials in the work environment can be costly and time consuming but is sometimes necessary to document the source of contaminated air. Inhalational fevers of all types are usually prevented by good maintenance of ventilation systems.

Nonspecific BRIs: Nonspecific BRIs are those for which a link between building-related exposure and illness is more difficult to prove. The term sick building syndrome has been used to refer to illnesses that occur in clusters within a building and that cause often nonspecific symptoms, including

- Itchy, irritated, dry or watery eyes
- Rhinorrhea or nasal congestion
- Throat soreness or tightness
- Dry itchy skin or unexplained rashes
- Headache, lethargy, or difficulty concentrating

Some building-related factors appear to account for symptoms in some instances. These factors include higher building temperature, higher humidity, and poor ventilation, typically with a failure to incorporate sufficient fresh air from outdoors. Patient factors, including female sex, history of atopy, increased attention to body sensations, worry about the meaning of symptoms, anxiety, depression, and occasionally mass hysteria, also seem to underlie experience of symptoms.

Byssinosis

Byssinosis is a form of reactive airways disease characterized by bronchoconstriction in cotton, flax, and hemp workers. The etiologic agent is unknown. Symptoms are chest tightness and dyspnea that worsen on the first day of the work week and subside as the week progresses. Diagnosis is based on history and pulmonary function test findings. Treatment includes avoidance of exposure and use of asthma drugs.

Etiology

Byssinosis occurs almost entirely in workers who contact unprocessed, raw cotton, especially those who are exposed to open bales or who work in cotton spinning or in the card room. Byssinosis can occur after acute exposure but usually occurs in workers with a history of chronic exposure. Evidence suggests that some agent in the cotton bract leads to bronchoconstriction. Although bacterial endotoxin is a likely cause, the absence of similar symptoms in other settings in which workers are exposed to endotoxin leaves some uncertainty. Prolonged exposure to cotton dust was once thought to cause emphysema, a theory now disproved. Chronic bronchitis symptoms are common among people exposed to cotton dust.

Symptoms and Signs

Symptoms are chest tightness and dyspnea that lessen with repeated exposure. Symptoms develop on the first day of work after a weekend or vacation and diminish or disappear by the end of the week. With repeated exposure over a period of years, chest tightness tends to return and persist through midweek and occasionally to the end of the week or as long as the person continues to work. This typical temporal pattern distinguishes byssinosis from asthma.

Signs of acute exposure are tachypnea and wheezing. Patients with more chronic exposure may have crackles.

Diagnosis

Diagnosis is based on history and pulmonary function tests that show typical airflow obstruction and a reduction in ventilatory capacity, especially if measured at the start and end of a first work shift. Hyperresponsiveness to methacholine is also often observed. Surveillance measures, including symptom reporting and spirometry in textile workers, can aid in early detection.

Treatment

Treatment includes avoidance or reduction of exposure and use of asthma drugs.

Coal Workers' Pneumoconiosis

(Anthracosis; Black Lung Disease; Coal Miner's Pneumoconiosis)

Coal workers' pneumoconiosis (CWP) is caused by inhalation of coal dust. Deposition of dust produces dust-laden macrophages around bronchioles (coal macules), occasionally causing focal bronchiolar emphysema. CWP usually causes no symptoms but can progress to progressive massive fibrosis (PMF) with impaired lung function. Diagnosis is based on history and chest x-ray findings. Treatment is generally supportive.

Etiology

CWP is caused by chronic inhalation of dust from high-carbon coal (anthracite and bituminous) and rarely graphite, typically over ≥ 20 yr. Inhalation of silica contained in coal may also contribute to clinical disease.

Pathophysiology

Alveolar macrophages engulf the dust, release cytokines that stimulate inflammation, and collect in lung interstitium around bronchioles and alveoli (coal macules). Coal nodules develop as collagen accumulates, and focal emphysema develops as bronchiole walls weaken and dilate. Fibrosis can occur but is usually limited to areas adjacent to coal macules. Distortion of lung architecture, airflow obstruction, and functional impairment are usually mild but can be highly destructive in some patients.

Two forms of CWP are described:

• Simple, with individual coal macules

• Complicated, with coalescence of macules and PMF

Patients with simple CWP develop PMF at a rate of about 1 to 2%. In PMF, nodules coalesce to form black, rubbery parenchymal masses usually in the upper posterior fields. The masses may encroach on and destroy vascular supply and airways or may cavitate. PMF can develop and progress even after exposure to coal dust has ceased. Despite the similarity of coal-induced PMF and conglomerate silicosis, the development of PMF in coal workers is unrelated to the silica content of the coal.

Complications: An association between CWP and features of rheumatoid arthritis (RA) is well-described. It is unclear whether CWP predisposes miners to developing RA, whether RA takes on a unique form in patients with CWP, or whether RA alters the response of miners to coal dust. Multiple rounded nodules in the lung appearing over a relatively short time (Caplan's syndrome) represent an immunopathologic response related to rheumatoid diathesis. Histologically, they resemble rheumatoid nodules but have a peripheral region of more acute inflammation. Patients with CWP are at a slightly increased risk of developing active TB and non-TB mycobacterial infections. Weak associations have been reported between CWP and progressive systemic sclerosis and stomach cancer.

Symptoms and Signs

CWP does not usually cause symptoms. Most chronic pulmonary symptoms in coal miners are caused by other conditions, such as industrial bronchitis due to coal dust or coincident emphysema due to smoking. Cough can be chronic and problematic in patients even after they leave the workplace, even in those who do not smoke.

PMF causes progressive dyspnea. Occasionally, patients cough up black sputum (melanoptysis), which occurs when PMF lesions rupture into the airways. PMF often progresses to pulmonary hypertension with right ventricular and respiratory failure.

Diagnosis

• History of exposure to coal dust

• Chest CT or chest x-ray

Diagnosis is based on a history of exposure and chest x-ray or chest CT appearance. In patients with CWP, x-ray or CT reveals diffuse, small, rounded opacities or nodules. The finding of at least one opacity > 10 mm suggests PMF. The specificity of the chest x-ray for PMF is low because up to one third of the lesions identified as being PMF turn out to be cancers, scars, or other disorders. Chest CT is more sensitive than chest x-ray for detecting coalescing nodules, early PMF, and cavitation.

Pulmonary function tests are nondiagnostic but are useful for characterizing lung function in patients in whom obstructive, restrictive, or mixed defects may develop. Because abnormalities of gas exchange occur in some patients with extensive simple CWP and in those with complicated CWP, baseline and periodic measures of diffusing capacity for carbon monoxide (DLCO) and ABG at rest and during exercise are recommended.

Because patients with CWP often have had exposure to both silica dust and coal dust, surveillance for TB is usually done. Patients with CWP should have annual tuberculin skin testing. In those with positive test results, sputum culture and cytology, CT, and bronchoscopy may be needed to confirm TB.

Treatment

• Sometimes supplemental O_2 and pulmonary rehabilitation

• Restriction from further exposure

Treatment is rarely necessary in simple CWP, although smoking cessation and TB surveillance are recommended. Patients with pulmonary hypertension, hypoxemia, or both are given supplemental O_2 therapy. Pulmonary rehabilitation can help more severely affected workers carry out activities of daily living. Workers with CWP, especially those with PMF, should be restricted from further exposure, especially to high concentrations of dust. TB is treated in accordance with current recommendations (see p. 1306).

Prevention

Preventive measures include eliminating exposure, stopping smoking, and giving pneumococcal and influenza vaccinations. CWP can be prevented by suppressing coal dust at the coal face. Despite long-standing regulations, exposures continue to occur in the mining trade. Respiratory masks provide only limited protection.

Occupational Asthma

Occupational asthma is reversible airway obstruction that develops after months to years of sensitization to an allergen encountered in the workplace. Symptoms are dyspnea, wheezing, cough, and, occasionally, upper respiratory allergic symptoms. Diagnosis is based on occupational history, including assessment of job activities, allergens in the work environment, and a temporal association between work and symptoms. Allergen skin testing and provocative inhalational challenge may be used in specialized centers but are usually unnecessary. Treatment involves removing the person from the work environment and using asthma drugs as needed.

Occupational asthma is development of asthma in a worker who has no previous history of asthma. Symptoms typically develop over months to years because of sensitization to an allergen encountered in the workplace. Once sensitized, the worker invariably responds to much lower concentrations of the allergen than that which initiated the response. Occupational asthma differs from occupationally aggravated asthma, which is an exacerbation or worsening of asthma in workers with preexisting asthma by single or repeated workplace exposures to pulmonary irritants such as dusts and fumes. Occupationally aggravated asthma, which is more common than occupational asthma, generally subsides with reduction of exposure and appropriate asthma treatment. It has a better prognosis and does not require the same level of clinical investigation of specific triggering allergens.

Several other airway diseases caused by inhalational workplace exposures can be distinguished from occupational and occupationally aggravated asthma.

In **reactive airways dysfunction syndrome** (RADS), which is nonallergenic, people with no history of asthma develop persistent, reversible airway obstruction after acute overexposure to irritant dust, fumes, or gas. Airway inflammation persists even after removal of the acute irritant, and the syndrome is indistinguishable from asthma.

In **reactive upper airways syndrome**, upper airway (ie, nasal, pharyngeal) mucosal symptoms develop after acute or repeated exposure to airways irritants.

In **irritant-associated vocal cord dysfunction**, which mimics asthma, abnormal apposition and closure of the vocal cords, especially during inspiration, occur after acute irritant inhalation.

In **industrial bronchitis** (irritant-induced chronic bronchitis), bronchial inflammation causes cough after acute or chronic irritant inhalation.

In **bronchiolitis obliterans**, bronchiolar damage occurs after acute inhalation of gases (eg, anhydrous ammonia). The 2 major forms are proliferative and constrictive. The constrictive form is more common and may or may not be associated with other forms of diffuse lung injury. Recently, cases of bronchiolitis obliterans have been reported in workers exposed to the chemical diacetyl during the manufacture of butter-flavored microwave popcorn. So-called popcorn workers' lung may occur in workers exposed to other flavorings and possibly in some consumers exposed to this chemical.

Etiology

Occupational asthma is caused by both immune- and non-immune-mediated mechanisms. Immune mechanisms involve IgE- and non-IgE-mediated hypersensitivity to workplace allergens. Hundreds of occupational allergens exist, ranging from low molecular weight chemicals to large proteins. Examples include grain dust, proteolytic enzymes used in detergent manufacturing, red cedar wood, isocyanates, formalin (rarely), antibiotics (eg, ampicillin, spiramycin), epoxy resins, and tea.

Non-immune-mediated inflammatory mechanisms cause direct irritation of the respiratory epithelium and upper airway mucosae.

Symptoms and Signs

Symptoms include shortness of breath, chest tightness, wheezing, and cough, often with upper respiratory symptoms such as sneezing, rhinorrhea, and tearing. Upper airway and conjunctival symptoms may precede the typical asthmatic symptoms by months or years. Symptoms may develop during work hours after specific dust or vapor exposure but often do not become apparent until several hours after leaving work, thereby making the association with occupational exposure less obvious. Nocturnal wheezing may be the only symptom. Often, symptoms disappear on weekends or during vacations, although with ongoing exposure temporal exacerbations and relief become less apparent.

Diagnosis

• Occupational history of allergen exposure

• Immunologic testing

• Sometimes inhalation challenge test

Diagnosis depends on recognizing the link between workplace allergens and asthma. Diagnosis is suspected on the basis of an occupational history of allergen exposure. A materials safety data sheet can be used to identify potential allergens, and substances listed can be used to direct immunologic testing (eg, skin prick, puddle, or patch testing) of suspected antigens to demonstrate that an agent in the workplace is affecting a person. An increase in bronchial hyperresponsiveness after exposure to the suspected antigen is also helpful in making the diagnosis.

In difficult cases, a carefully controlled inhalation challenge test done in the laboratory confirms the cause of the airway obstruction. Such procedures should be done only at centers experienced in inhalation challenge testing and capable of monitoring and treating the sometimes severe reactions that can occur. Pulmonary function tests or peak expiratory flow measurements that show decreasing airflow during work are further evidence that occupational exposure is causative. Methacholine challenge tests can be used to establish the degree of airway hyperreactivity. Sensitivity to methacholine may decrease after exposure to the occupational allergen has ceased.

Differentiation from idiopathic asthma is generally based on the pattern of symptoms, demonstration that allergens are present in the workplace, and the relationship between exposure to allergens and symptoms and physiologic worsening.

Treatment

Treatment is the same as that for idiopathic asthma, including inhaled bronchodilators and corticosteroids (see p. 1873). Treatment should also include removal of the patient from ongoing exposure to the causative agent.

Prevention

Dust suppression is essential. However, elimination of all instances of sensitization and clinical disease may not be possible. Once sensitized, patients with occupational asthma may react to extremely low levels of airborne allergen. Patients who return to environments in which the allergen persists generally have a poorer prognosis, with more respiratory symptoms, more abnormal lung physiology, a greater need for drugs, and more frequent and severe exacerbations. Whenever possible, a symptomatic person should be removed from a setting known to cause symptoms. If exposure continues, symptoms tend to persist. Occupational asthma can sometimes be cured if it is diagnosed early and exposure ceases.

Silicosis

Silicosis is caused by inhalation of unbound (free) crystalline silica dust and is characterized by nodular pulmonary fibrosis. Chronic silicosis initially causes no symptoms or only mild dyspnea but over years can advance to involve most of the lung and cause dyspnea, hypoxemia, pulmonary hypertension, and respiratory impairment. Diagnosis is based on history and chest x-ray findings. No effective treatment exists except supportive care and, for severe cases, lung transplantation.

Etiology

Silicosis, the oldest known occupational pulmonary disease, is caused by inhalation of tiny particles of silicon dioxide in the form of unbound (free) crystalline silica (usually quartz) or, less commonly, by inhalation of silicates, minerals containing silicon dioxide bound to other elements, such as talc. Workers at greatest risk are those who move or blast rock and sand (miners, quarry workers, stonecutters) or who use silica-containing rock or sand abrasives (sand blasters; glass makers; foundry, gemstone, and ceramic workers; potters). Coal miners are at risk of mixed silicosis and coal workers' pneumoconiosis (see p. 1977).

Factors that influence the likelihood of development of silicosis include

- Duration and intensity of exposure
- Form of silicon (exposure to the crystalline form poses greater risk than the bound form)
- Surface characteristics (exposure to the uncoated form poses greater risk than the coated form)
- Rapidity of inhalation after the dust is fractured and becomes airborne (exposure immediately after fracturing poses greater risk than delayed exposure)

Pathophysiology

Alveolar macrophages engulf inhaled free silica particles and enter lymphatics and interstitial tissue. The macrophages cause release of cytokines (tumor necrosis factor-α, IL-1), growth factors (tumor growth factor-β), and oxidants, stimulating parenchymal inflammation, collagen synthesis, and, ultimately, fibrosis.

When the macrophages die, they release the silica into interstitial tissue around the small bronchioles, causing formation of the pathognomonic silicotic nodule. These nodules initially contain macrophages, lymphocytes, mast cells, fibroblasts with disorganized patches of collagen, and scattered birefringent particles that are best seen by polarized light microscopy. As they mature, the centers of the nodules become dense balls of fibrotic scar with a classic onion-skin appearance and are surrounded by an outer layer of inflammatory cells. In low-intensity or short-term exposures, these nodules remain discrete and do not compromise lung function (simple chronic silicosis). But with higher-intensity or more prolonged exposures (complicated chronic silicosis), these nodules coalesce and cause progressive fibrosis and reduction of lung volumes (total lung capacity, ventilatory capacity) on pulmonary function tests, or they coalesce, sometimes forming large conglomerate masses (called progressive massive fibrosis).

Chronic silicosis is the most common form of the disorder and generally develops only after exposure over decades.

Acute silicosis and the rarer **accelerated silicosis** are caused by intense silica dust exposure over short periods (several months or years). Mononuclear cells infiltrate alveolar septa, and alveolar spaces fill with a proteinaceous material that stains periodic acid-Schiff (PAS) positive and is similar to that found in pulmonary alveolar proteinosis (silicoproteinosis—see p. 1962). The occupational history of acute exposure is needed to distinguish silicoproteinosis from the idiopathic variety.

Conglomerate (complicated) silicosis is the advanced form of chronic or accelerated silicosis and is characterized by widespread masses of fibrosis, typically in the upper lung zones.

Complications: Patients with silicosis are at risk of other disorders:

• TB

• Lung cancer

• Progressive systemic sclerosis (scleroderma)

• Possibly RA

All patients with silicosis are at about a 30-fold increased risk of pulmonary TB or nontubercular mycobacterial disease and are more likely to develop both pulmonary and extrapulmonary manifestations. Increased risk may result from impaired macrophage function and an increased risk of activation of latent infection. People exposed to silica but without silicosis have 3 times the risk of developing TB compared with the nonexposed general population.

Other complications include spontaneous pneumothorax, broncholithiasis, and tracheobronchial obstruction. Emphysema is a common finding in areas immediately peripheral to conglomerate nodules and in areas of progressive massive fibrosis.

Symptoms and Signs

Chronic silicosis is often asymptomatic, but many patients eventually develop dyspnea during exertion that progresses to dyspnea at rest. Productive cough, when present, may be due to silicosis, coexisting chronic occupational (industrial) bronchitis, or smoking. Breath sounds diminish as the disorder progresses, and pulmonary consolidation, pulmonary hypertension, and respiratory failure with or without right ventricular failure may develop in advanced disease.

Patients with accelerated silicosis experience the same symptoms as those with chronic silicosis, but symptoms develop over a shorter period.

Acute silicosis patients experience rapid progression of dyspnea, weight loss, and fatigue with diffuse bilateral crackles. Respiratory failure often develops within 2 yr.

Conglomerate silicosis causes severe, chronic respiratory symptoms.

Diagnosis

• Occupational history of silica exposure

• Chest CT or chest x-ray

• Sometimes tissue biopsy for confirmation

• Adjunctive tests for distinguishing silicosis from other disorders

Imaging: Silicosis is usually recognized on the basis of chest x-ray or CT appearance in patients with a history of exposure. CT is more sensitive than x-ray, especially when helical CT and high-resolution techniques are used. In most cases, chest CT is preferable because it is more sensitive for detecting silicosis as well as the transition from simple to conglomerate silicosis. Chest CT can also better distinguish asbestosis from silicosis, although this differentiation can usually be made on the basis of chest x-ray and exposure history. In patients who develop RA, 3- to 5-mm pulmonary rheumatoid nodules are visible on chest x-ray or CT.

Chronic silicosis produces multiple 1- to 3-mm rounded opacities or nodules recognized on chest x-ray or CT, usually in upper lung fields. Severity is graded on a standardized scale developed by the International Labor Organization, in which specially trained readers examine the chest x-ray for size and shape of opacities, concentration of opacities (profusion), and pleural changes. An equivalent scale does not exist for CT appearance. Calcified hilar and mediastinal lymph nodes are common and occasionally

resemble eggshells. Pleural thickening is uncommon unless a severe parenchymal disease abuts the pleura. Rarely, calcified pleural thickening occurs in patients with little parenchymal involvement. Bullae commonly form around the conglomerate masses. Tracheal deviation may occur when the masses become large and cause volume loss. True cavities may indicate TB.

Numerous disorders resemble chronic silicosis on x-ray; they include welders' siderosis, hemosiderosis, sarcoidosis, chronic beryllium disease, hypersensitivity pneumonitis, coal workers' pneumoconiosis, miliary TB, fungal pulmonary diseases, and metastatic cancer. Eggshell calcifications in hilar and mediastinal lymph nodes may help distinguish silicosis from other pulmonary disorders but are not a pathognomonic finding and are not commonly present.

Accelerated silicosis resembles chronic silicosis on x-ray but develops more rapidly.

Acute silicosis is recognized by rapid progression of symptoms. X-ray findings include diffuse alveolar bibasilar opacities representing fluid-filled alveoli. On CT, areas of ground-glass density consisting of reticular infiltration and areas of patchy increased attenuation and inhomogeneity occur. These areas are best observed on thin-section, spiral CT views. The multiple rounded opacities of chronic and accelerated silicosis are not characteristic of acute silicosis.

Conglomerate silicosis is recognizable by confluent opacities > 10 mm in diameter against a background of chronic silicosis findings.

Adjunctive tests: Tuberculin skin testing, sputum culture and cytology, PET, and bronchoscopy all may assist in distinguishing silicosis from disseminated TB or cancer.

Pulmonary function tests and measures of gas exchange (diffusing capacity for carbon monoxide [DLCO], ABGs) are not diagnostic but help monitor progression. Early chronic silicosis may manifest with reduced lung volumes that are at the lower end of the predicted range and with normal functional residual capacity and residual volume. In conglomerate silicosis, pulmonary function tests reveal decreased lung volumes, decreased DLCO, and airway obstruction. ABGs show hypoxemia usually without CO_2 retention. Measurement of gas exchange during exercise, using pulse oximetry or preferably an indwelling arterial catheter, is one of the most sensitive measures of pulmonary impairment.

Antinuclear antibodies and elevated rheumatoid factor are detectable in some patients and are suggestive but not diagnostic of a coexisting connective tissue disorder (eg, scleroderma, RA).

Treatment

• Sometimes whole lung lavage

• Sometimes oral corticosteroids

• Rarely lung transplantation

• Empiric use of bronchodilators and inhaled corticosteroids for obstruction

• Removal from further exposure

Whole lung lavage may be useful in some cases of acute silicosis. Whole lung lavage can reduce the total mineral dust load in the lungs of patients with chronic silicosis. Some studies have shown short-term reduction in symptoms after lavage, but controlled trials have not been done. Anecdotal evidence supports the use of oral corticosteroids in acute and accelerated silicosis. Lung transplantation is a last resort.

Patients with airway obstruction may be treated empirically with bronchodilators and inhaled corticosteroids. Patients should be monitored and treated for hypoxemia to forestall pulmonary hypertension. Pulmonary rehabilitation may help patients carry out activities of daily living. Workers who develop silicosis should be removed from further exposure.

Management of TB is the same as for other patients with TB except that longer courses are usually recommended because relapse is more common in patients with silicotuberculosis.

Prevention

The most effective preventive interventions occur at an industrial rather than clinical level and include dust suppression, process isolation, ventilation, and use of non-silicacontaining abrasives. Respiratory masks provide imperfect protection and, although helpful, are not an adequate solution. Surveillance of exposed workers with respiratory questionnaires, spirometry, and chest x-rays is recommended. Frequency of surveillance depends to some degree on the expected intensity of the exposure. Other preventive measures include smoking cessation and pneumococcal and influenza vaccination.

Physicians must be alert to the risk of TB and nontuberculous mycobacterial infections in silica-exposed patients, especially miners. People exposed to silica should have annual tuberculin testing. Those with a positive skin test should have sputum culture for TB. In some cases, CT and bronchoscopy may be needed to confirm TB. Patients with a positive tuberculin test and negative TB cultures should be given isoniazid chemoprophylaxis in keeping with standard guidelines for tuberculin reactors.

Irritant Gas Inhalation Injury

Irritant gases are those which, when inhaled, dissolve in the water of the respiratory tract mucosa and cause an inflammatory response, usually from the release of acidic or alkaline radicals. Irritant gas exposures predominantly affect the airways, causing tracheitis, bronchitis, and bronchiolitis. Other inhaled agents may be directly toxic (eg, cyanide, carbon monoxide) or cause harm simply by displacing O_2 and producing asphyxia (eg, methane, carbon dioxide).

The effect of inhaling irritant gases depends on the extent and duration of exposure and on the specific agent. Chlorine, phosgene, sulfur dioxide, hydrogen chloride or sulfide, nitrogen dioxide, ozone, and ammonia are among the most important irritant gases. Hydrogen sulfide is also a potent cellular toxin, blocking the cytochrome system and inhibiting cellular respiration. A common exposure involves mixing household ammonia with cleansers containing bleach; the irritant gas chloramine is released.

Acute Exposure

Acute exposure to high concentrations of toxic gas over a short time is characteristic of industrial accidents resulting from a faulty valve or pump in a gas tank or occurring during gas transport. Many people may be exposed and affected. The release of methyl isocyanate from a chemical plant in Bhopal, India in 1984 killed > 2000 people.

Respiratory damage is related to the concentration of the gas and its solubility.

More water-soluble gases (eg, chlorine, ammonia, sulfur dioxide, hydrogen chloride) dissolve in the upper airway and immediately cause mucous membrane irritation, which may alert people to the need to escape the exposure. Permanent damage to the upper respiratory tract, distal airways, and lung parenchyma occurs only if escape from the gas source is impeded.

Less soluble gases (eg, nitrogen dioxide, phosgene, ozone) may not dissolve until they are well into the respiratory tract, often reaching the lower airways. These agents are less likely to produce early warning signs (phosgene in low concentrations has a pleasant odor), are more likely to cause severe bronchiolitis, and often have a lag of ≥ 12 h before symptoms of pulmonary edema develop.

Complications: The most serious immediate complication is ARDS, which usually occurs within 24 h. Patients with significant lower airway involvement may develop bacterial infection.

Ten to 14 days after acute exposure to some agents (eg, ammonia, nitrogen oxides, sulfur dioxide, mercury), some patients develop bronchiolitis obliterans progressing to ARDS. Bronchiolitis obliterans with organized pneumonia can ensue when granulation tissue accumulates in the terminal airways and

alveolar ducts during the body's reparative process. A minority of these patients develop late pulmonary fibrosis.

Symptoms and Signs

Soluble irritant gases cause severe burning and other manifestations of irritation of the eyes, nose, throat, trachea, and major bronchi. Marked cough, hemoptysis, wheezing, retching, and dyspnea are common. The upper airway may be obstructed by edema, secretions, or laryngospasm. Severity is generally doserelated. Nonsoluble gases cause fewer immediate symptoms but can cause dyspnea or cough.

Patients who develop ARDS have worsening dyspnea and increasing O_2 requirements.

Diagnosis

• History of exposure

• Chest x-ray

Diagnosis is usually obvious from the history. Patients should have a chest x-ray and pulse oximetry. Chest x-ray findings of patchy or confluent alveolar consolidation usually indicate pulmonary edema.

CT is used to evaluate patients with late-developing symptoms. Those with bronchiolitis obliterans that progresses to respiratory failure manifest a pattern of bronchiolar thickening and a patchy mosaic of hyperinflation.

Prognosis

Most people recover fully, but some have persistent lung injury with reversible airway obstruction (reactive airways dysfunction syndrome) or pulmonary fibrosis; smokers may be at greater risk.

Treatment

• Removal from exposure and 24-h observation

• Bronchodilators and supplemental O_2

• Sometimes inhaled racemic epinephrine, endotracheal intubation, and mechanical ventilation

Management does not differ by specific inhaled agent but rather by symptoms. Patients should be moved into fresh air and given supplemental O_2. Treatment is directed toward ensuring adequate oxygenation and alveolar ventilation. Bronchodilators and O_2 therapy may suffice in less severe cases. Severe airflow obstruction is managed with inhaled racemic epinephrine, endotracheal intubation or tracheostomy, and mechanical ventilation. The efficacy of corticosteroid therapy (eg, prednisone 45 to 60 mg once/day for 1 to 2 wk) is unproved, but it is frequently used.

Because of the risk of ARDS, any patient with respiratory tract symptoms after toxic inhalation should be observed for 24 h.

After the acute phase has been managed, physicians must remain alert to the development of reactive airways dysfunction syndrome, bronchiolitis obliterans with or without organized pneumonia, pulmonary fibrosis, and delayed-onset ARDS.

Prevention

Care in handling gases and chemicals is the most important preventive measure. The availability of adequate respiratory protection (eg, gas masks with a self-contained air supply) for rescuers is also very

important; rescuers without protective gear who rush in to extricate a victim often succumb themselves.

Chronic Exposure

Low-level continuous or intermittent exposure to irritant gases or chemical vapors may lead to chronic bronchitis, although the role of such exposure is especially difficult to substantiate in smokers.

Chronic inhalational exposure to some agents (eg, bis[chloromethyl]ether, certain metals) causes lung and other cancers (eg, liver angiosarcomas after vinyl chloride monomer exposure).

Chapter 202. Pulmonary Hypertension

Introduction

Pulmonary hypertension is increased pressure in the pulmonary circulation. It has many secondary causes; some cases are idiopathic. In pulmonary hypertension, pulmonary vessels become constricted, hypertrophied, and fibrosed. Severe pulmonary hypertension leads to right ventricular overload and failure. Symptoms are fatigue, exertional dyspnea, and, occasionally, chest discomfort and syncope. Diagnosis is made by measuring pulmonary artery pressure. Treatment is with vasodilators and diuretics. In some advanced cases, lung transplantation is an option. Prognosis is poor overall if a treatable secondary cause is not found.

Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥ 25 mm Hg at rest or ≥ 35 mm Hg during exercise.

Etiology

Many conditions and drugs cause pulmonary hypertension. A small number of cases occur sporadically, unrelated to any identifiable disorder; these cases are termed idiopathic pulmonary arterial hypertension. The most common overall causes of pulmonary hypertension include

• Left heart failure, including diastolic dysfunction

• Parenchymal lung disease with hypoxia

• Miscellaneous: Sleep apnea, connective tissue disorders, and pulmonary embolism

Pulmonary hypertension is currently classified into 5 groups (see Table 202-1) based on a number of pathologic, physiologic, and clinical factors. In the first group (pulmonary arterial hypertension), the primary disorder affects the small pulmonary arterioles.

Pathophysiology

Pathophysiologic mechanisms that cause pulmonary hypertension include increased

[**Table 202-1.** Classification of Pulmonary Hypertension]

pulmonary vascular resistance and increased pulmonary venous pressure. Pulmonary vascular resistance can be caused by obliteration of the pulmonary vascular bed or hypoxic vasoconstriction. Pulmonary hypertension is characterized by variable vasoconstriction, smooth muscle hypertrophy, and vascular wall remodeling. Vasoconstriction is thought to be due in part to enhanced activity of thromboxane and endothelin-1 (both vasoconstrictors) and reduced activity of prostacyclin and nitric oxide (both vasodilators). The increased pulmonary vascular pressure that results from vascular obstruction further injures the endothelium. Injury activates coagulation at the intimal surface, which may worsen the hypertension. Thrombotic coagulopathy due to increased activity of plasminogen activator inhibitor type 1 and fibrinopeptide A and decreased tissue plasminogen activator activity may also contribute. Focal coagulation at the endothelial surface should not be confused with chronic thromboembolic pulmonary hypertension, in which pulmonary hypertension is caused by organized pulmonary emboli.

In most patients, pulmonary hypertension eventually leads to right ventricular hypertrophy followed by dilation and right ventricular failure.

Symptoms and Signs

Progressive exertional dyspnea and easy fatigability occur in almost all patients. Atypical chest discomfort and exertional light-headedness or presyncope may accompany dyspnea. These symptoms are due primarily to insufficient cardiac output. Raynaud's syndrome occurs in about 10% of patients with

idiopathic pulmonary arterial hypertension; the majority are women. Hemoptysis is rare but may be fatal. Hoarseness due to recurrent laryngeal nerve compression by an enlarged pulmonary artery (ie, Ortner syndrome) also occurs rarely.

In advanced disease, signs may include right ventricular heave, widely split 2nd heart sound (S_2), an accentuated pulmonic component (P_2) of S_2, a pulmonary ejection click, a right ventricular 3rd heart sound (S_3), tricuspid murmur, and jugular vein distention. Liver congestion and peripheral edema are common late manifestations.

Diagnosis

• Exertional dyspnea

• Initial confirmation: Chest x-ray, spirometry, ECG, echocardiography, and CBC

• Identification of underlying disorder: Ventilation-perfusion scan or CT angiography, pulmonary function testing, polysomnography, HIV testing, liver function testing, and antinuclear antibodies

• Determination of severity: Right heart catheterization

Pulmonary hypertension is suspected in patients with significant exertional dyspnea who are otherwise relatively healthy and have no history or signs of other diseases known to cause pulmonary symptoms.

Patients initially undergo chest x-ray, spirometry, and ECG to identify more common causes of dyspnea, followed by Doppler echocardiography to assess right ventricular and pulmonary artery pressures as well as to detect structural heart disease that might be causing pulmonary hypertension. CBC is obtained to document the presence or absence of polycythemia, anemia, and thrombocytopenia.

The most common x-ray finding in pulmonary hypertension is enlarged hilar vessels that rapidly prune into the periphery and a right ventricle that fills the anterior airspace on lateral view. Spirometry and lung volumes may be normal or detect mild restriction, and diffusing capacity for carbon monoxide (DLCO) is usually reduced. Common ECG findings include right axis deviation, R > S in V_1, $S_1Q_3T_3$, and peaked P waves.

Additional tests are obtained as indicated to diagnose secondary causes that are not apparent clinically. These tests include

• Ventilation-perfusion scanning or CT angiography to detect thromboembolic disease

• Pulmonary function tests to identify obstructive or restrictive lung disease

• Serum serologic tests to gather evidence for or against rheumatologic disease

Chronic thromboembolic pulmonary hypertension is suggested by CT or lung scan findings and is confirmed by arteriography. CT angiography is useful to evaluate proximal clot and fibrotic encroachment of the vascular lumen. Other tests, such as HIV testing, liver function tests, and polysomnography, are done in the appropriate clinical context.

When the initial evaluation detects no conditions known to be associated with pulmonary hypertension, pulmonary artery catheterization is necessary to measure right atrial and ventricular, pulmonary artery, and pulmonary artery occlusion pressures; cardiac output; and left ventricular diastolic pressure. Right-sided O_2 saturation should be measured to exclude atrial septal defect. Although finding a mean pulmonary arterial pressure of > 25 mm Hg in the absence of an underlying disorder identifies pulmonary hypertension, most patients with pulmonary arterial hypertension present with substantially higher pressure (eg, mean of 60 mm Hg). Vasodilating drugs, such as inhaled nitric oxide, IV epoprostenol, or adenosine, are often administered during catheterization. Decreasing right-sided pressures in response to these drugs may help in the choice of drugs for treatment. Lung biopsy, once widely done, is neither

needed nor recommended because of its associated high morbidity and mortality.

Once pulmonary hypertension is diagnosed, the patient's family history should be reviewed to detect possible genetic transmission (eg, premature deaths in otherwise healthy members of the extended family). In familial pulmonary arterial hypertension, genetic counseling is needed to advise mutation carriers of the risk of disease (about 20%) and to advocate serial screening with echocardiography. Testing for mutations in the *BMPR2* gene in idiopathic pulmonary arterial hypertension may have a future role.

Prognosis

Untreated patients have a median survival of 2.5 yr. Cause of death is usually sudden death in the context of right ventricular failure. Five-year survival for epoprostenol-treated patients is 54%, whereas that for the small minority of patients who respond to Ca channel blockers is > 90%. Signs predictive of poor survival include low cardiac output, higher pulmonary artery and right atrial pressures, lack of response to vasodilators, heart failure, hypoxemia, and reduced overall physical functioning. Patients with the connective tissue disorder systemic sclerosis are at high risk of pulmonary arterial hypertension and have a poor prognosis.

Treatment

- Avoidance of activities that may exacerbate the condition (eg, cigarette smoking, use of sympathomimetics)

- Idiopathic and familial pulmonary arterial hypertension: Ca channel blockers; IV epoprostenol; inhaled, oral, or sc prostacyclin analogs; oral endothelin-receptor antagonists; and/or oral phosphodiesterase inhibitors

- Secondary pulmonary arterial hypertension: Treatment of the underlying disorder

- Rarely lung transplantation

- Adjunctive therapy: Supplemental O_2, diuretics, and/or anticoagulants

Patients are encouraged to avoid activities or circumstances that may exacerbate their condition. Examples include cigarette smoking, exposure to high altitudes, and drugs that lead to vasoconstriction, such as sympathomimetics.

Pulmonary arterial hypertension, group 1: Treatment is rapidly evolving. Oral Ca channel blockers reduce pulmonary arterial pressure or pulmonary vascular resistance in about 5% of patients. No differences in efficacy exist among Ca channel blocker types, though most specialists avoid verapamil because of its negative inotropic effects. Response to Ca channel blockers is a favorable prognostic sign, and patients who respond should continue this treatment. Patients who do not respond at the time of diagnosis are given other drugs.

IV epoprostenol, a prostacyclin analog, improves function and lengthens survival even in patients who are unresponsive to a vasodilator during catheterization. Epoprostenol is currently the most effective therapy for pulmonary arterial hypertension. Disadvantages are the need for continuous central catheter infusion and frequent, troubling adverse effects, including flushing, diarrhea, and bacteremia associated with the indwelling central catheter. Prostacyclin analogs that are inhaled (iloprost) or given sc or IV (treprostinil) are available.

Two oral endothelin-receptor antagonists, bosentan and ambrisentan, are available in the US; these drugs are useful in some patients, generally those with milder disease at diagnosis. Oral sildenafil is also effective.

Lung transplantation offers the only hope of cure but has high morbidity because of rejection, infection, and bronchiolitis obliterans. The 5-yr survival rate is 60%. Lung transplantation is reserved for patients

with New York Heart Association class IV disease (defined as dyspnea associated with minimal activity, leading to bed to chair limitations) in whom all therapies have failed and who meet other health criteria to be a transplant candidate.

Many patients require adjunctive therapies to treat heart failure, including diuretics, and most should receive warfarin unless there is a contraindication.

Pulmonary hypertension, groups 2 to 5: Primary treatment involves management of the underlying disorder. Patients with left-sided heart disease may need surgery for valvular disease. Patients with lung disorders and hypoxia benefit from supplemental O_2 as well as treatment of the primary disorder. Patients with severe pulmonary hypertension secondary to chronic thromboembolic disease should be considered for pulmonary thromboendarterectomy. During cardiopulmonary bypass, an organized endothelialized thrombus is dissected along the pulmonary trunk in a procedure more complex than acute surgical embolectomy. This procedure cures pulmonary hypertension in a substantial percentage of patients and restores cardiopulmonary function; operative mortality is < 10% in patients treated in centers that have extensive experience.

Portopulmonary Hypertension

Portopulmonary hypertension is pulmonary arterial hypertension associated with portal hypertension without other secondary causes.

Pulmonary hypertension occurs in patients with various conditions that involve portal hypertension with or without cirrhosis. Portopulmonary hypertension occurs less commonly than the hepatopulmonary syndrome in patients with chronic liver disease (3.5 vs 12%).

Presenting symptoms are dyspnea and fatigue. Chest pain and hemoptysis can also occur. Patients have physical findings and ECG abnormalities consistent with pulmonary hypertension and may develop evidence of cor pulmonale (elevated jugular venous pulse, edema). Tricuspid regurgitation is common.

The diagnosis is suspected based on echocardiography findings and confirmed by right heart catheterization.

Treatment is the same as that of pulmonary arterial hypertension except that hepatotoxic drugs should be avoided. Some patients benefit from vasodilator therapy. The underlying liver disease is a major determinant of outcome. Portopulmonary hypertension is a relative contraindication to liver transplantation because of increased morbidity and mortality from the procedure. However, in some patients who receive a transplant, particularly those with mild pulmonary hypertension, pulmonary hypertension regresses. Some centers consider transplantation in patients who have mean pulmonary arterial pressures < 35 mm Hg after a trial of vasodilator therapy.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is hypoxemia caused by pulmonary microvascular vasodilation in patients with portal hypertension; dyspnea and hypoxemia are worse in the upright position.

The hepatopulmonary syndrome results from the formation of microscopic intrapulmonary arteriovenous dilations in patients with chronic liver disease. The mechanism is unknown but is thought to be due to increased hepatic production or decreased hepatic clearance of vasodilators, possibly nitric oxide. The vascular dilations cause overperfusion relative to ventilation, leading to hypoxemia. Because the lesions frequently are more numerous at the lung bases, the hepatopulmonary syndrome causes platypnea (dyspnea) and orthodeoxia (hypoxemia), which occur in the seated or upright position and are relieved by recumbency. Most patients also have characteristic findings of chronic liver disease, such as spider angiomas. About 20% of patients present with pulmonary symptoms alone.

Diagnosis

• Pulse oximetry

• Contrast echocardiography and sometimes other imaging

Hepatopulmonary syndrome should be suspected in a patient with known liver disease who reports dyspnea (particularly platypnea). Patients with clinically significant symptoms should have pulse oximetry. If the syndrome is advanced, ABGs should be measured with the patient breathing room air and 100% O_2 to determine shunt fraction.

A useful diagnostic test is contrast echocardiography. Intravenous microbubbles from agitated saline that are normally trapped in the pulmonary capillaries rapidly (ie, within 7 heartbeats) traverse the lung and appear in the left atrium. Similarly, IV technetium-99m-labeled albumin may traverse the lungs and appear in the kidneys and brain. Pulmonary angiography may reveal a diffusely fine or blotchy vascular configuration. Angiography is generally not needed unless thromboembolism is suspected.

Treatment

• Supplemental O_2

The main treatment is supplemental O_2 for symptoms. Other therapies, such as somatostatin to inhibit vasodilation, are of modest benefit in only some patients. Coil embolization is virtually impossible because of the number and size of the lesions. Inhaled nitric oxide synthesis inhibitors may be a future treatment option. Hepatopulmonary syndrome may regress after liver transplantation or if the underlying liver disease subsides. Prognosis is poor without treatment (survival < 2 yr).

Chapter 203. Diffuse Alveolar Hemorrhage and Pulmonary-Renal Syndromes

Introduction

Some alveolar hemorrhage syndromes are associated with glomerulonephritis; then, the disorder is called pulmonary-renal syndrome (see p. 1990).

Diffuse Alveolar Hemorrhage Syndrome

Diffuse alveolar hemorrhage syndrome is persistent or recurrent pulmonary hemorrhage. There are numerous causes, but autoimmune disorders are the most common. Most patients present with dyspnea, cough, hemoptysis, and new alveolar infiltrates. Diagnostic tests are directed at the suspected cause. Treatment is with immunosuppressants for patients with autoimmune causes and respiratory support if needed.

Diffuse alveolar hemorrhage syndrome is not a specific entity but is a syndrome that suggests a differential diagnosis and a specific sequence of testing.

Pathophysiology

Diffuse alveolar hemorrhage syndrome results from widespread damage of the pulmonary small vessels, leading to blood collection within the alveoli, thereby disrupting O_2 and CO_2 exchange. The specific pathophysiology and manifestations vary depending on cause. For example, isolated pauci-immune pulmonary capillaritis is a small-vessel vasculitis limited to the lung; its only manifestation is alveolar hemorrhage affecting people aged 18 to 35 yr. Idiopathic pulmonary hemosiderosis is diffuse alveolar hemorrhage syndrome with no detectable underlying disorder; it occurs mainly in children < 10 yr and is thought to be due to a defect in the alveolar capillary endothelium, possibly due to autoimmune injury.

Etiology

Many disorders can cause alveolar hemorrhage; they include

- Autoimmune disorders (eg, systemic vasculitides, Goodpasture's syndrome, antiphospholipid antibody syndrome)
- Pulmonary infections (eg, invasive aspergillosis, hantavirus infection)
- Toxic exposures (eg, trimellitic anhydride, isocyanates, crack cocaine, certain pesticides)
- Drug reactions (eg, propylthiouracil, diphenylhydantoin, amiodarone, methotrexate, nitrofurantoin, bleomycin, montelukast, infliximab)
- Cardiac disorders (eg, mitral stenosis)
- Coagulation disorders caused by diseases or anticoagulant drugs
- Isolated pauci-immune pulmonary capillaritis
- Idiopathic pulmonary hemosiderosis
- Bone marrow or solid organ transplantation

Symptoms and Signs

Symptoms and signs of milder diffuse alveolar hemorrhage syndrome are dyspnea, cough, and fever; however, many patients present with acute respiratory failure, sometimes leading to death. Hemoptysis is common but may be absent in up to one third of patients. Children with idiopathic pulmonary

hemosiderosis may have failure to thrive.

There are no specific physical examination findings.

Other manifestations depend on the underlying disorder (eg, diastolic murmur in patients with mitral stenosis).

Diagnosis

• Chest x-ray

• Sometimes bronchoscopy

• Serologic and other tests to diagnose the cause

Diagnosis is suggested by dyspnea, cough, and hemoptysis accompanied by chest x-ray findings of diffuse bilateral alveolar infiltrates. Bronchoscopy with bronchoalveolar lavage (BAL) may be done to confirm the diagnosis when manifestations are atypical or an airway source of hemorrhage has not been excluded. Specimens show blood with numerous erythrocytes and siderophages; lavage fluid typically remains hemorrhagic even after sequential sampling.

Evaluation of the cause: Further testing for the cause should be done. Urinalysis is indicated to exclude glomerulonephritis; serum BUN and creatinine also should be done. Other routine tests include CBC, coagulation studies, platelet counts, and serologic tests (antinuclear antibody, anti-double-stranded DNA (anti-dsDNA), antiglomerular basement membrane [anti-GBM] antibodies, antineutrophil cytoplasmic antibodies [ANCA], antiphospholipid antibody) to look for underlying disorders; perinuclear-ANCA (p-ANCA) titers are elevated in some cases of isolated pauciimmune pulmonary capillaritis. Diagnosis of idiopathic pulmonary hemosiderosis involves demonstration of iron deficiency anemia and hemosiderin-laden macrophages in BAL fluid or lung biopsy specimens when there is no evidence of small-vessel vasculitis (pulmonary capillaritis) or of other diagnoses.

Other tests depend on clinical context. Pulmonary function tests may be done to document lung function. They may show increased diffusing capacity for carbon monoxide (DLCO) due to increased uptake of carbon monoxide by intra-alveolar Hb; however, this finding, which is consistent with hemorrhage, does not assist with establishing a diagnosis. Echocardiography may be indicated to exclude mitral stenosis. BAL is done when diffuse alveolar hemorrhage is suspected. Lung or kidney biopsy is frequently needed when a cause remains unclear or the progression of disease is too rapid to await the results of serologic testing.

Prognosis

Patients can require mechanical ventilation and even die as a result of hemorrhage-associated respiratory failure. Recurrent alveolar hemorrhage causes pulmonary hemosiderosis and fibrosis, both of which develop when ferritin aggregates within alveoli and exerts toxic effects. COPD occurs in some patients with recurrent diffuse alveolar hemorrhage secondary to microscopic polyarteritis.

Treatment

• Corticosteroids

• Sometimes cyclophosphamide or plasmapheresis

• Supportive measures

Treatment involves correcting the cause. Corticosteroids and possibly cyclophosphamide are used to treat vasculitides, connective tissue disorders, and Goodpasture's syndrome. Plasmapheresis may be used to treat Goodpasture's syndrome. Corticosteroids are also used to treat idiopathic pulmonary hemosiderosis; immunosuppressants are added for nonresponders. Several studies have reported

successful use of recombinant activated human factor VII in treating alveolar hemorrhage.

Other possible management measures include supplemental O_2, bronchodilators, reversal of any coagulopathy, intubation with bronchial tamponade, protective strategies for the less involved lung, and mechanical ventilation.

Pulmonary-Renal Syndrome

Pulmonary-renal syndrome (PRS) is diffuse alveolar hemorrhage and glomerulonephritis occurring simultaneously. Cause is almost always an autoimmune disorder. Diagnosis is by serologic tests and sometimes lung and renal biopsy. Treatment typically includes immunosuppression with corticosteroids and cytotoxic drugs.

PRS is not a specific entity but is a syndrome that suggests a differential diagnosis and a specific sequence of testing.

Pulmonary pathology is small-vessel vasculitis involving arterioles, venules, and, frequently, alveolar capillaries. Renal pathology is small-vessel vasculitis resulting in a form of focal proliferative glomerulonephritis.

Etiology

PRS is almost always a manifestation of an underlying autoimmune disorder. Goodpasture's syndrome is the prototype cause, but PRS can also be caused by SLE, Wegener's granulomatosis, microscopic polyangiitis, and, less commonly, by other vasculitides and connective tissue disorders (see Table 203-1).

PRS is less commonly a manifestation of IgA-mediated disorders, such as IgA nephropathy or Henoch-Schonlein purpura, and of immune complex-mediated renal disease, such as essential mixed cryoglobulinemia. Rarely, rapidly progressive glomerulonephritis alone can cause PRS through a mechanism involving renal failure, volume overload, and pulmonary edema with hemoptysis.

Symptoms and Signs

Symptoms and signs typically include dyspnea, cough, fever, and hemoptysis in combination with peripheral edema and hematuria or other signs of glomerulonephritis.

Diagnosis

• Serologic testing

• Sometimes lung and renal biopsies

PRS is suspected in patients with hemoptysis not obviously attributable to other causes (eg, pneumonia, carcinoma, bronchiectasis), particularly when hemoptysis is accompanied by diffuse parenchymal infiltrates and findings suggesting renal disease.

Initial testing includes urinalysis for evidence of hematuria and red cell casts (suggesting

[**Table 203-1.** Causes of Pulmonary-Renal Syndrome]

glomerulonephritis), serum creatinine for renal function assessment, and CBC for evidence of anemia. Chest x-ray is done if not yet obtained.

Serum antibody testing may help distinguish some causes, as in the following:

• Antiglomerular basement membrane antibodies: Goodpasture's syndrome

- Antibodies to double-stranded DNA and reduced serum complement levels: SLE
- Antineutrophil cytoplasmic antibodies (ANCA) to proteinase-3 (PR3-ANCA or cytoplasmic ANCA [c-ANCA]): Wegener's granulomatosis
- ANCA to myeloperoxidase (MPO-ANCA, or perinuclear ANCA [p-ANCA]): Microscopic polyangiitis

Definitive diagnosis requires lung biopsy with findings of small-vessel vasculitis and renal biopsy with findings of glomerulonephritis with or without antibody deposition.

Pulmonary function tests and bronchoalveolar lavage are not diagnostic of PRS but can be used to help confirm diffuse alveolar hemorrhage in patients with glomerulonephritis and pulmonary infiltrates but without hemoptysis. Lavage fluid that remains hemorrhagic after sequential sampling establishes diffuse alveolar hemorrhage, especially in the context of falling Hct.

Treatment

- Corticosteroids
- Sometimes cyclophosphamide

Immunosuppression is the cornerstone of treatment. Standard induction-remission regimens include pulse IV methylprednisolone (500 to 1000 mg IV once/day for 3 to 5 days). As life-threatening features subside, the corticosteroid dose can be reduced; 1 mg/kg prednisone (or equivalent) po once/day is given for the first month, then tapered over the next 3 to 4 mo. Cyclophosphamide should be added to corticosteroid therapy in critically ill patients with generalized disease, at a dose of 0.5 to 1 g/m^2 IV given as a pulse once/mo or orally (1 to 2 mg/kg once/day).

Transition to maintenance therapy may occur 6 to 12 mo after the initiation of induction therapy or after clinical remission. Maintenance therapy includes low-dose corticosteroids coupled with cytotoxic agents. However, relapse may occur despite ongoing therapy.

Goodpasture's Syndrome

(Anti-GBM Antibody Disease)

Goodpasture's syndrome, a subtype of PRS, is an autoimmune syndrome of alveolar hemorrhage and glomerulonephritis caused by circulating anti-glomerular basement membrane (anti-GBM) antibodies. Goodpasture's syndrome most often develops in genetically susceptible people who smoke cigarettes, but hydrocarbon exposure and viral respiratory infections are additional possible triggers. Symptoms are dyspnea, cough, fatigue, hemoptysis, and hematuria. Goodpasture's syndrome is suspected in patients with hemoptysis or hematuria and is confirmed by the presence of anti-GBM antibodies in the blood or in a renal biopsy specimen. Prognosis is good when treatment is begun before onset of respiratory or renal failure. Treatment includes plasmapheresis, corticosteroids, and immunosuppressants, such as cyclophosphamide.

Pathophysiology

Goodpasture's syndrome is the combination of glomerulonephritis with alveolar hemorrhage and anti-GBM antibodies. Goodpasture's syndrome most often manifests as diffuse alveolar hemorrhage and glomerulonephritis together but can occasionally cause glomerulonephritis (10 to 20%) or pulmonary disease (10%) alone. Men are affected more often than women.

Anti-GBM antibodies are directed against the noncollagenous (NC-1) domain of the α3 chain of type IV collagen, which occurs in highest concentration in the basement membranes of renal and pulmonary capillaries. Environmental exposures—cigarette smoking, viral URI, and hydrocarbon solvent inhalation most commonly and pneumonia less commonly—expose alveolar capillary antigens to circulating antibody

in genetically susceptible people, most notably those with HLA-DRw15, -DR4, and -DRB1 alleles. Circulating anti-GBM antibodies bind to basement membranes, fix complement, and trigger a cell-mediated inflammatory response, causing glomerulonephritis, pulmonary capillaritis, or both.

Symptoms and Signs

Hemoptysis is the most prominent symptom; however, hemoptysis may not occur in patients with hemorrhage, and patients may present with only chest x-ray infiltrates or with infiltrates and respiratory distress, respiratory failure, or both. Dyspnea, cough, fatigue, fever, and weight loss are common. Up to 40% of patients have gross hematuria, although pulmonary hemorrhage may precede renal manifestations by weeks to years.

Signs vary over time and range from clear lungs on auscultation to crackles and rhonchi. Some patients have peripheral edema due to renal failure and pallor due to anemia.

Diagnosis

• Serum anti-GBM antibody tests

• Sometimes renal biopsy

Definitive diagnosis of Goodpasture's syndrome requires demonstration of serum anti-GBM antibodies by indirect immunofluorescence testing or, when available, direct enzyme-linked immunosorbent assay (ELISA) with recombinant or human NC-1 α3. However, ANCA testing is positive (in a peripheral pattern) in only 25% of patients with Goodpasture's syndrome.

Renal biopsy is indicated in patients with glomerulonephritis (hematuria, proteinuria, red cell casts detected with urinalysis, renal insufficiency, or a combination of these findings). A rapidly progressive focal segmental necrotizing glomerulonephritis with crescent formation is found in biopsy specimens in patients with Goodpasture's syndrome and all other causes of PRS. Immunofluorescence staining of renal or lung tissue classically shows linear IgG deposition along the glomerular or alveolar capillaries. IgG deposition also occurs in the kidneys of patients with diabetes or with fibrillary glomerulonephritis (a rare disorder causing PRS), but GBM binding of antibodies in these disorders is nonspecific and does not occur in linear patterns.

Prognosis

Goodpasture's syndrome is often rapidly progressive and can be fatal if prompt recognition and treatment are delayed; prognosis is good when treatment begins before onset of respiratory or renal failure. Long-term morbidity is related to the degree of renal impairment at presentation; patients requiring dialysis at presentation and those with > 50% crescents in the biopsy specimen (who often will require dialysis) usually survive for < 2 yr unless kidney transplantation is done. Hemoptysis may be a good prognostic sign because it leads to earlier detection; the minority of patients who are ANCA-positive respond better to treatment. Relapse occurs in a small number and is linked to continued tobacco use and respiratory infection. In patients with end-stage renal disease who receive kidney transplantation, disease can recur in the graft.

Treatment

• Plasmapheresis

• Corticosteroids and cyclophosphamide

Immediate survival in patients with pulmonary hemorrhage and respiratory failure is linked to airway control; endotracheal intubation and mechanical ventilation are recommended for patients with borderline ABGs and impending respiratory failure. Patients with significant renal impairment may require dialysis or kidney transplantation.

Treatment is daily or every-other-day plasmapheresis for 2 to 3 wk using 4-L exchanges to remove anti-GBM antibodies, combined with a corticosteroid (usually methylprednisolone 1 g IV over 20 min once/day or every other day for 3 doses followed by prednisone (1 mg/kg po once/day for 3 wk, then titrated down to 20 mg po once/day for 6 to 12 mo) and cyclophosphamide (2 mg/kg po or IV once/day for 6 to 12 mo) to prevent formation of new antibodies. Therapy can be tapered when pulmonary and renal function stop improving.

Chapter 204. Mediastinal and Pleural Disorders

Introduction

Mediastinal and pleural disorders include masses, mediastinitis, pleural effusion, pleural fibrosis and calcification, pneumomediastinum, pneumothorax, and viral pleuritis.

Mediastinal Masses

Mediastinal masses are caused by a variety of cysts and tumors; likely causes differ by patient age and by location of the mass (anterior, middle, or posterior mediastinum). The masses may be asymptomatic (in adults) or cause obstructive respiratory symptoms (in children). Testing involves CT with biopsy and adjunctive tests as needed. Treatment differs by cause.

Etiology

Mediastinal masses are divided into those that occur in the anterior, middle, and posterior mediastinum. The anterior mediastinum extends from the sternum to the pericardium and brachiocephalic vessels posteriorly. The middle mediastinum lies between the anterior and posterior mediastinum. The posterior mediastinum is bounded by the pericardium and trachea anteriorly and the vertebral column posteriorly.

Adults: In adults, thymomas and lymphomas (both Hodgkin and non-Hodgkin) are the most common anterior lesions, lymph node enlargement and vascular masses are the most common middle lesions, and neurogenic tumors and esophageal abnormalities are the most common posterior lesions. For other causes, see
Fig. 204-1.

Children: In children, the most common mediastinal masses are neurogenic tumors and cysts. For other causes, see
Table 204-1.

Symptoms and Signs

Many mediastinal masses are asymptomatic. In general, malignant lesions and masses in children are much more likely to cause symptoms. The most common symptoms are chest pain and weight loss. Lymphomas may manifest with fever and weight loss. In children, mediastinal masses are more likely to cause tracheobronchial compression and stridor or symptoms of recurrent bronchitis or pneumonia.

Symptoms and signs also depend on location. Large anterior mediastinal masses may cause dyspnea when patients are supine. Lesions in the middle mediastinum may compress blood vessels or airways, causing the superior

[**Fig. 204-1.** Some causes of mediastinal masses in adults.]

[**Table 204-1.** Some Causes of Mediastinal Masses in Children]

vena cava syndrome or airway obstruction. Lesions in the posterior mediastinum may encroach on the esophagus, causing dysphagia or odynophagia.

Diagnosis

• Chest x-ray

• CT

• Sometimes tissue examination

Mediastinal masses are most often incidentally discovered on chest x-ray or other imaging tests during an

examination for chest symptoms. Additional diagnostic testing, usually imaging and biopsy, is indicated to determine etiology.

CT with IV contrast is the most valuable imaging technique. With thoracic CT, normal variants and benign tumors, such as fat- and fluid-filled cysts, can be distinguished from other processes. A definitive diagnosis can be obtained for many mediastinal masses with needle aspiration or needle biopsy. Fine-needle aspiration techniques usually suffice for carcinomatous lesions, but a cutting-needle biopsy should be done whenever lymphoma, thymoma, or a neural mass is suspected. If ectopic thyroid tissue is considered, thyroid-stimulating hormone is measured.

Treatment

Treatment depends on etiology. Some benign lesions, such as pericardial cysts, can be observed. Most malignant tumors should be removed surgically, but some, such as lymphomas, are best treated with chemotherapy. Granulomatous disease should be treated with the appropriate antimicrobial drug.

Mediastinitis

Mediastinitis is inflammation of the mediastinum. Acute mediastinitis usually results from esophageal perforation or median sternotomy. Symptoms include severe chest pain, dyspnea, and fever. The diagnosis is confirmed by chest x-ray or CT. Treatment is with antibiotics (eg, clindamycin plus ceftriaxone) and sometimes surgery.

The 2 most common causes of acute mediastinitis are esophageal perforation and median sternotomy.

Esophageal perforation may complicate esophagoscopy or insertion of a Sengstaken-Blakemore or Minnesota tube (for esophageal variceal bleeding). Rarely, it results from forceful vomiting (Boerhaave's syndrome). Another possible cause is swallowing caustic substances (eg, lye, certain button batteries). Certain pills or esophageal ulcers (eg, in AIDS patients with esophagitis) can contribute.

Patients with esophageal perforation become acutely ill within hours, with severe chest pain and dyspnea due to mediastinal inflammation. Diagnosis is usually obvious from clinical presentation and a history of instrumentation or of another risk factor. The diagnosis should also be considered in patients who are very ill, have chest pain, and may have a risk factor that they cannot describe (eg, in intoxicated patients who may have vomited forcefully but do not remember and in preverbal children who may have ingested a button battery). The diagnosis is confirmed by chest x-ray or CT showing air in the mediastinum.

Treatment is with parenteral antibiotics selected to be effective against oral and GI flora (eg, clindamycin 450 mg IV q 6 h plus ceftriaxone 2 g once/day, for at least 2 wk). Patients who have severe mediastinitis with pleural effusion or pneumothorax require emergency exploration of the mediastinum with primary repair of the esophageal tear and drainage of the pleural space and mediastinum.

Median sternotomy: This procedure is complicated by mediastinitis in about 1% of cases. Patients most commonly present with wound drainage or sepsis. Diagnosis is based on finding infected fluid obtained by a needle aspiration through the sternum. Treatment consists of immediate surgical drainage, debridement, and parenteral broad-spectrum antibiotics. Mortality approaches 50% in some series.

Chronic fibrosing mediastinitis: This condition is usually is due to TB or histoplasmosis but can be due to sarcoidosis, silicosis, or other fungal diseases. An intense fibrotic process develops, leading to compression of mediastinal structures that can cause the superior vena cava syndrome, tracheal narrowing, or obstruction of the pulmonary arteries or veins.

Diagnosis is based on CT. If the cause is TB, anti-TB therapy is indicated. Otherwise, no known treatment is beneficial, but insertion of vascular or airway stents can be considered.

Pleural Effusion

Pleural effusions are accumulations of fluid within the pleural space. They have multiple causes

and usually are classified as transudates or exudates. Detection is by physical examination and chest x-ray; thoracentesis and pleural fluid analysis are often required to determine cause. Asymptomatic transudates require no treatment. Symptomatic transudates and almost all exudates require thoracentesis, chest tube drainage, pleurodesis, pleurectomy, or a combination.

Normally, 10 to 20 mL of pleural fluid, similar in composition to plasma but lower in protein (< 1.5 g/dL), is spread thinly over visceral and parietal pleurae, facilitating movement between the lung and chest wall. The fluid enters the pleural space from systemic capillaries in the parietal pleurae and exits via parietal pleural stomas and lymphatics. Pleural fluid accumulates when too much fluid enters or too little exits the pleural space.

Etiology

Pleural effusions are usually categorized as transudates or exudates based on laboratory characteristics of the fluid (see Table 204-2). Whether unilateral or bilateral, a transudate can usually be treated without extensive evaluation, whereas the cause of an exudate requires investigation. There are numerous causes (see Table 204-3).

Transudative effusions are caused by some combination of increased hydrostatic pressure and decreased plasma oncotic pressure. Heart failure is the most common cause, followed by cirrhosis with ascites and hypoalbuminemia, usually due to the nephrotic syndrome.

Exudative effusions are caused by local processes leading to increased capillary permeability resulting in exudation of fluid, protein, cells, and other serum constituents. Causes are numerous; the most common are pneumonia, cancer, pulmonary embolism, viral infection, and TB. Yellow nail syndrome is a rare disorder causing chronic exudative pleural effusions, lymphedema, and dystrophic yellow nails—all thought to be the result of impaired lymphatic drainage.

[**Table 204-2.** Criteria for Identifying Exudative Pleural Effusions]

[**Table 204-3.** Causes of Pleural Effusion]

Chylous effusion (chylothorax) is a milky white effusion high in triglycerides caused by traumatic or neoplastic (most often lymphomatous) damage to the thoracic duct. Chylous effusion also occurs with the superior vena cava syndrome.

Chyliform (cholesterol or pseudochylous) effusions resemble chylous effusions but are low in triglycerides and high in cholesterol. Chyliform effusions are thought to be due to release of cholesterol from lysed RBCs and neutrophils in long-standing effusions when absorption is blocked by the thickened pleura.

Hemothorax is bloody fluid (pleural fluid Hct > 50% peripheral Hct) in the pleural space due to trauma or, rarely, as a result of coagulopathy or after rupture of a major blood vessel, such as the aorta or pulmonary artery.

Empyema is pus in the pleural space. It can occur as a complication of pneumonia, thoracotomy, abscesses (lung, hepatic, or subdiaphragmatic), or penetrating trauma with secondary infection. Empyema necessitatis is soft-tissue extension of empyema leading to chest wall infection and external drainage.

Trapped lung is a lung encased by a fibrous peel caused by empyema or tumor. Because the lung cannot expand, the pleural pressure becomes more negative than normal, increasing transudation of fluid from parietal pleural capillaries. The fluid characteristically is borderline between a transudate and an exudate; ie, the biochemical values are within 15% of the cutoff levels for Light's criteria (see Table 204-2).

Iatrogenic effusions can be caused by migration or misplacement of a feeding tube into the trachea or perforation of the superior vena cava by a central venous catheter, leading to infusion of tube feedings or IV solution into the pleural space.

Effusions with no obvious cause are often due to occult pulmonary emboli, TB, or cancer. Etiology is unknown for about 15% of effusions even after extensive study; many of these effusions are thought to be due to viral infection.

Symptoms and Signs

Some pleural effusions are asymptomatic and are discovered incidentally during physical examination or on chest x-ray. Many cause dyspnea, pleuritic chest pain, or both. Pleuritic chest pain, a vague discomfort or sharp pain that worsens during inspiration, indicates inflammation of the parietal pleura. Pain is usually felt over the inflamed site, but referred pain is possible. The posterior and peripheral portions of the diaphragmatic pleura are supplied by the lower 6 intercostal nerves, and irritation there may cause pain in the lower chest wall or abdomen that may simulate intra-abdominal disease. Irritation of the central portion of the diaphragmatic pleura, innervated by the phrenic nerves, causes pain referred to the neck and shoulder.

Physical examination reveals absent tactile fremitus, dullness to percussion, and decreased breath sounds on the side of the effusion. These findings can also be caused by pleural thickening. With large-volume effusions, respiration is usually rapid and shallow. A pleural friction rub, although infrequent, is the classic physical sign. The friction rub varies from a few intermittent sounds that may simulate crackles to a fully developed harsh grating, creaking, or leathery sound synchronous with respiration, heard during inspiration and expiration. Friction sounds adjacent to the heart (pleuropericardial rub) may vary with the heartbeat and may be confused with the friction rub of pericarditis. Pericardial rub is best heard over the left border of the sternum in the 3rd and 4th intercostal spaces, is characteristically a to-and-fro sound synchronous with the heartbeat, and is not influenced significantly by respiration. Sensitivity and specificity of the physical examination for detecting effusion are probably low.

Diagnosis

• Chest x-ray

• Pleural fluid analysis

• Sometimes helical CT or other tests

Pleural effusion is suspected in patients with pleuritic pain, unexplained dyspnea, or suggestive signs. Diagnostic tests are indicated to document the presence of pleural fluid and to determine its cause (see Fig. 204-2).

Presence of effusion: Chest x-ray is the first test done to confirm the presence of pleural fluid. The lateral upright chest x-ray should be examined when a pleural effusion is suspected. In an upright x-ray, 75 mL of fluid blunts the posterior costophrenic angle. Blunting of the lateral costophrenic angle usually requires about 175 mL but may take as much as 500 mL. Larger pleural effusions opacify portions of the hemithorax and may cause mediastinal shift; effusions > 4 L may cause complete opacification of the hemithorax and mediastinal shift to the contralateral side.

Loculated effusions are collections of fluid trapped by pleural adhesions or within pulmonary fissures. Lateral decubitus x-rays, chest CT, or ultrasonography should be done if it is unclear whether an x-ray density represents fluid or parenchymal infiltrates or whether suspected fluid is loculated or free-flowing;

[**Fig. 204-2.** Diagnosis of pleural effusion.]

these tests are more sensitive than upright x-rays and can detect fluid volumes < 10 mL. Loculated effusions, particularly those in the horizontal or oblique fissure, can be confused with a solid pulmonary mass (pseudotumor). They may change shape and size with changes in the patient's position and amount

of pleural fluid.

CT is not routinely indicated but is valuable for evaluating the underlying lung parenchyma for infiltrates or masses when the lung is obscured by the effusion or when the detail on chest x-rays is insufficient and for distinguishing loculated fluid from a solid mass.

Cause of effusion: Thoracentesis (see p. 1864) should be done in almost all patients who have pleural fluid that is ≥ 10 mm in thickness on CT, ultrasonography, or lateral decubitus x-ray and that is new or of uncertain etiology. In general, the only patients who do not require thoracentesis are those who have heart failure with symmetric pleural effusions and no chest pain or fever; in these patients, diuresis can be tried, and thoracentesis avoided unless effusions persist for ≥ 3 days.

Despite common practice, chest x-ray need not be repeated after thoracentesis unless patients develop symptoms suggesting pneumothorax (dyspnea or chest pain) or unless there is reason to suspect that air may have entered the pleural space during the procedure. Thoracentesis and subsequent pleural fluid analysis often are not necessary for pleural effusions that are chronic, have a known cause, and cause no symptoms.

Ultrasonography is helpful for identifying the site for thoracentesis when the amount of pleural fluid is small, the fluid is loculated, or blind thoracentesis is unsuccessful.

Pleural fluid analysis is done to diagnose the cause of pleural effusion. Analysis begins with visual inspection, which can

• Distinguish bloody and chylous (or chyliform) from other effusions

• Identify purulent effusions strongly suggestive of empyema

• Identify viscous fluid, which is characteristic of some mesotheliomas

Fluid should always be sent for total protein, LDH, cell count and cell differential, Gram stain, and aerobic and anaerobic bacterial cultures. Other tests (glucose, cytology, TB fluid markers [adenosine deaminase or interferon-γ], amylase, mycobacterial and fungal stains and cultures) are used in appropriate clinical settings.

Fluid chemistries help distinguish transudates from exudates; multiple criteria exist, but not one perfectly discriminates between the 2 types. When Light's criteria are used (see Table 204-2), serum LDH and total protein levels should be measured as close as possible to the time of thoracentesis for comparison with pleural fluid. Light's criteria correctly identify almost all exudates but misidentify about 20% of transudates as exudates. If transudative effusion is suspected (eg, due to heart failure or cirrhosis) and none of the biochemical measurements are > 15% above the cutoff levels for Light's criteria, the difference between serum and the pleural fluid protein is measured. If the difference is > 3.1 g/dL, the patient probably has a transudative effusion.

If the diagnosis remains unclear after pleural fluid analysis, helical CT is indicated to look for pulmonary emboli, pulmonary infiltrates, or mediastinal lesions. Findings of pulmonary emboli indicate the need for long-term anticoagulation; parenchymal infiltrates, the need for bronchoscopy; and mediastinal lesions, the need for transthoracic needle aspiration or mediastinoscopy. However, helical CT requires patients to hold their breath for ≥ 24 sec, and not all patients can comply. If helical CT is unrevealing, observation is the best course unless the patient has a history of cancer, weight loss, persistent fever, or other findings suggesting cancer or TB, in which case thoracoscopy may be indicated. Needle biopsy of the pleura can be done when thoracoscopy is unavailable. When thoracoscopy is unrevealing, an open thoracotomy must sometimes be done. Most patients with exudative effusions should have a PPD placed with a control on the other arm, but TB can neither be diagnosed if the PPD result is positive nor definitively excluded if it is negative, so pleural biopsy is generally needed.

Treatment

• Treatment of symptoms and underlying disorder

• Drainage of some symptomatic effusions

• Other treatments for parapneumonic and malignant effusions

The effusion itself generally does not require treatment if it is asymptomatic when the underlying disorder is treated because many effusions resorb spontaneously, especially those due to uncomplicated pneumonias, pulmonary embolism, or surgery. Pleuritic pain can usually be managed with NSAIDs or other oral analgesics. At times, a short course of oral opioids is required.

Thoracentesis is sufficient treatment for many symptomatic effusions and can be repeated for effusions that reaccumulate. Removal of fluid can be continued until the patient develops chest tightness, chest pain, or severe coughing.

Effusions that are chronic, recurrent, and causing symptoms can be treated with pleurodesis or by intermittent drainage with an indwelling catheter (see p. 2003). Effusions caused by pneumonia and cancer may require additional specific measures.

Parapneumonic effusion and empyema: In patients with adverse prognostic factors (pH < 7.20, glucose < 60 mg/dL, positive Gram stain or culture, loculations), the effusion should be completely drained via thoracentesis or tube thoracostomy. If complete drainage is impossible, a thrombolytic (fibrinolytic) drug (eg, urokinase 100,000 units or tissue plasminogen activator 10 mg in 100 mL saline solution) can be administered intrapleurally, but the effectiveness of this intervention is unproved. If attempts at drainage are unsuccessful, thoracoscopy should be done to lyse adhesions and remove fibrous tissue coating the lung to allow the lung to expand. If thoracoscopy is unsuccessful, thoracotomy with surgical decortication (eg, removal of scar, clot, or fibrous membrane surrounding the lung) is necessary.

Malignant pleural effusion: If dyspnea caused by malignant pleural effusion is relieved by thoracentesis but fluid reaccumulates (with dyspnea), chronic (intermittent) drainage or pleurodesis is indicated. Asymptomatic effusions and effusions causing dyspnea unrelieved by thoracentesis do not require additional procedures.

Indwelling catheter drainage is the preferred approach for ambulatory patients because hospitalization is not necessary for catheter insertion and the pleural fluid can be drained intermittently into vacuum bottles. Pleurodesis is done by instilling a sclerosing agent into the pleural space to fuse the visceral and parietal pleura and eliminate the space. The most effective and commonly used sclerosing agents are talc, doxycycline, and bleomycin delivered via chest tube or thoracoscopy. Pleurodesis is contraindicated if the mediastinum has shifted toward the side of the effusion or if the lung does not expand after a chest tube is inserted.

Shunting of pleural fluid to the peritoneum (pleuroperitoneal shunt) is useful for patients with malignant effusion in whom pleurodesis is unsuccessful and in patients who have trapped lung.

Pleural Fibrosis and Calcification

Pleural fibrosis and calcification are usually benign sequelae of pleural inflammation or asbestos exposure.

Pleural fibrosis and calcification can be either postinflammatory or asbestos related. These disorders are suspected and diagnosed based on imaging studies.

Postinflammatory: Pleural inflammation commonly causes acute pleural thickening due to fibrosis. In most cases, the thickening resolves almost completely. Some patients are left with minor degrees of pleural thickening, which usually causes no symptoms or impairment of lung function. Occasionally, the lung becomes encased with a thick, fibrous pleural peel that limits expansion, pulls the mediastinum toward the side of disease, and impairs pulmonary function. Chest x-ray shows asymmetry of the lungs

with thickened pleura (trapped lung). Differentiating localized pleural thickening from loculated pleural fluid may be difficult on x-ray, but this differentiation is easily made with CT.

Pleural fibrosis after inflammation can, on occasion, calcify. Calcification produces a dense image on the chest x-ray and almost always involves the visceral pleura. Postinflammatory calcifications are invariably unilateral.

Asbestos-related: Exposure to asbestos can lead to focal, plaquelike pleural fibrosis, at times with calcification, occurring up to ≥ 20 yr after the initial exposure. Diagnosis is usually by chest-x-ray. The diameter of the plaques can vary from several millimeters to 10 cm. Any pleural or pericardial surface can be affected, but asbestos-related pleural plaques are usually in the lower two thirds of the thorax and are bilateral. Calcification most often affects the parietal and diaphragmatic pleura and spares the costophrenic sulci and apices. Calcification may be the only evidence of exposure. Dense pleural fibrosis surrounding the entire lung and >1 cm in thickness can also follow asbestos exposure.

Pneumomediastinum

Pneumomediastinum is air in mediastinal interstices.

The 3 main causes of pneumomediastinum are alveolar rupture with dissection of air into the mediastinum, esophageal perforation, and esophageal or bowel rupture with dissection of air from the neck or the abdomen into the mediastinum.

The primary symptom is substernal chest pain which can, on occasion, be severe. Physical examination may show subcutaneous emphysema, usually in the suprasternal notch, along with a crunching or clicking noise synchronous with the heartbeat; this noise is best heard over the heart when the patient is in the left lateral decubitus position (Hamman's sign).

The diagnosis is confirmed by chest x-ray, which shows air in the mediastinum.

Treatment usually is not necessary, although tension pneumomediastinum with compression of mediastinal structures (rare) can be relieved with needle aspiration, leaving the needle open to the atmosphere as is done with tension pneumothorax. Hospital admission is required if pneumomediastinum is secondary to esophageal or bowel rupture but not necessarily if secondary to alveolar rupture.

Pneumothorax

Pneumothorax is air in the pleural space causing partial or complete lung collapse. Pneumothorax can occur spontaneously or result from trauma or medical procedures. Diagnosis is based on clinical criteria and chest x-ray. Most pneumothoraces require transcatheter aspiration or tube thoracostomy.

Intrapleural pressure is normally negative (less than atmospheric pressure) because of inward lung and outward chest wall recoil. In pneumothorax, air enters the pleural space from outside the chest or from the lung itself via mediastinal tissue planes or direct pleural perforation. Intrapleural pressure increases, and lung volume decreases.

Etiology

Primary spontaneous pneumothorax occurs in patients without underlying pulmonary disease, classically in tall, thin young men in their teens and 20s. It is thought to be due to spontaneous rupture of subpleural apical blebs or bullae that result from smoking or that are inherited. It generally occurs at rest, although some cases occur during activities involving reaching or stretching. Primary spontaneous pneumothorax also occurs during diving and high-altitude flying because of unequally transmitted pressure changes in the lung.

Secondary spontaneous pneumothorax occurs in patients with underlying pulmonary disease. It most often results from rupture of a bleb or bulla in patients with severe COPD (forced expiratory volume in 1

sec [FEV_1] < 1 L), HIV-related *Pneumocystis jirovecii* infection, cystic fibrosis, or any underlying pulmonary parenchymal disease (see Table 204-4). Secondary spontaneous pneumothorax is more serious than primary spontaneous pneumothorax because it occurs in patients whose underlying lung disease decreases their pulmonary reserve. Catamenial pneumothorax is a rare form of secondary spontaneous pneumothorax that occurs within 48 h of the onset of menstruation in premenopausal women and sometimes in postmenopausal women taking estrogen. The cause is intrathoracic endometriosis, possibly due to migration of peritoneal endometrial tissue through diaphragmatic defects or embolization through pelvic veins.

[**Table 204-4.** Causes of Secondary Spontaneous Pneumothorax]

Traumatic pneumothorax is a common complication of penetrating or blunt chest injuries.

Tension pneumothorax is a pneumothorax causing a progressive rise in intrapleural pressure to levels that become positive throughout the respiratory cycle and collapse the lung, shift the mediastinum, and impair venous return to the heart. Air continues to get into the pleural space but cannot exit. Without appropriate treatment, the impaired venous return can cause systemic hypotension and respiratory and cardiac arrest (pulseless electrical activity) within minutes. Tension pneumothorax most commonly occurs in patients receiving positive-pressure ventilation (with mechanical ventilation or particularly during resuscitation). Rarely, it is a complication of traumatic pneumothorax, when a chest wound acts as a one-way valve that traps increasing volumes of air in the pleural space during inspiration.

Iatrogenic pneumothorax is caused by medical interventions, including transthoracic needle aspiration, thoracentesis, central venous catheter placement, mechanical ventilation, and cardiopulmonary resuscitation.

Symptoms and Signs

Small pneumothoraces are occasionally asymptomatic. Symptoms of pneumothoraces include dyspnea and pleuritic chest pain. Dyspnea may be sudden or gradual in onset depending on the rate of development and size of the pneumothorax. Pain can simulate pericarditis, pneumonia, pleuritis, pulmonary embolism, musculoskeletal injury (when referred to the shoulder), or an intra-abdominal process (when referred to the abdomen). Pain can also simulate cardiac ischemia, although typically the pain of cardiac ischemia is not pleuritic.

Physical findings classically consist of absent tactile fremitus, hyperresonance to percussion, and decreased breath sounds on the affected side. If the pneumothorax is large, the affected side may be enlarged with the trachea visibly shifted to the opposite side. With tension pneumothorax, hypotension can occur.

Diagnosis

• Upright inspiratory chest x-ray

The diagnosis is suspected in stable patients with dyspnea or pleuritic chest pain and is confirmed with upright inspiratory chest x-ray. Radiolucent air and the absence of lung markings juxtaposed between a shrunken lobe or lung and the parietal pleura are diagnostic of pneumothorax. Tracheal deviation and mediastinal shift occur with large pneumothoraces.

The size of a pneumothorax is defined as the percentage of the hemithorax that is vacant. This percentage is estimated by taking 1 minus the ratio of the cubes of the width of the lung and hemithorax. For example, if the width of the hemithorax is 10 cm and the width of the lung is 5 cm, the ratio is $5^3/10^3 = 0.125$. Thus, the size of the pneumothorax is about 1 minus 0.125, or 87.5%. If adhesions are present between the lung and the chest wall, the lung does not collapse symmetrically, the pneumothorax may appear atypical or loculated, and the calculation is not accurate.

Small pneumothoraces (eg, < 10%) are sometimes overlooked on chest x-ray. Conditions that mimic

pneumothorax radiographically include emphysematous bullae, skinfolds, folded bed sheets, and overlap of stomach or bowel markings on lung fields.

Tension pneumothorax is suspected in patients with sudden, unexplained hypotension and dyspnea or some risk factor, particularly positive pressure ventilation. If such a patient also has signs of pneumothorax, such as decreased breath sounds and hyperresonance to percussion, tension pneumothorax should be assumed.

Treatment

• Immediate needle decompression for tension pneumothoraces

• Observation and follow-up x-ray for small, asymptomatic primary spontaneous pneumothoraces

• Catheter aspiration for large or symptomatic primary spontaneous pneumothoraces

• Tube thoracostomy for secondary and traumatic pneumothoraces

Patients should receive supplemental O_2 until chest x-ray results are available because O_2 accelerates pleural reabsorption of air. Treatment then depends on the type, size, and effects of pneumothorax. Primary spontaneous pneumothorax that is < 20% and that does not cause respiratory or cardiac symptoms can be safely observed without treatment if follow-up chest x-rays obtained at about 6 and 48 h show no progression. Larger or symptomatic primary spontaneous pneumothoraces should be evacuated by catheter aspiration. Tube thoracostomy is an alternative.

Catheter aspiration is accomplished by insertion of a small-bore (about 7 to 9 French) IV or pigtail catheter into the chest in the 2nd intercostal space at the midclavicular line. The catheter is attached to a 3-way stopcock and syringe. Air is withdrawn from the pleural space through the stopcock into the syringe and expelled into the room. The process is repeated until the lung re-expands or until 4 L of air are removed. If the lung expands, the catheter can be removed or kept in place attached to a one-way Heimlich valve (thus permitting ambulation), and the patient need not be hospitalized. If the lung does not expand, a chest tube should be inserted, and the patient should be hospitalized. Primary spontaneous pneumothoraces can also be managed initially with a chest tube attached to a water seal without or with suction. Patients with primary spontaneous pneumothoraces should also undergo smoking cessation counseling.

Secondary and traumatic pneumothoraces are generally treated with tube thoracostomy. (see p. 1866). Symptomatic patients with iatrogenic pneumothoraces are best managed initially with aspiration.

Tension pneumothorax is a medical emergency, and time should not be wasted confirming the diagnosis with a chest x-ray. It should be treated immediately by inserting a 14- or 16-gauge needle with a catheter through the chest wall in the 2nd intercostal space at the midclavicular line. The sound of high-pressure air escaping confirms diagnosis. The catheter can be left open to air or attached to a Heimlich valve. Emergency decompression must be followed immediately by tube thoracostomy, after which the catheter is removed.

Complications

The 3 main problems encountered when treating pneumothorax are air leaks, failure of the lung to expand, and re-expansion pulmonary edema.

Air leaks are usually due to the primary defect—ie, continued leakage of air from the lung into the pleural space—but can be due to air leaking around the chest tube insertion site if the site is not properly sutured and sealed. Air leaks are more common in secondary than in primary spontaneous pneumothorax. Most resolve spontaneously in < 1 wk.

Failure of the lung to re-expand is usually due to a persistent air leak, an endobronchial obstruction, a trapped lung, or a malpositioned chest tube. Thoracoscopy or thoracotomy should be considered if an air

leak or an incompletely expanded lung persists beyond 1 wk.

Re-expansion pulmonary edema occurs when the lung is rapidly expanded, as occurs when a chest tube is connected to negative pressure after the lung has been collapsed for > 2 days. Treatment is supportive, with O_2, diuretics, and cardiopulmonary support as needed.

Prevention

Recurrence approaches 50% in the 3 yr after initial spontaneous pneumothorax. The best preventive procedure is video-assisted thoracic surgery (VATS) in which blebs are stapled and pleurodesis is done with pleural abrasion, parietal pleurectomy, or talc insufflation; in some medical centers, thoracotomy is still used. These procedures are recommended when catheter aspiration fails with spontaneous pneumothorax, when pneumothorax recurs, or when patients have secondary spontaneous pneumothorax. Recurrence after these procedures is < 5%. If thoracoscopy cannot be done or is contraindicated, chemical pleurodesis through a chest tube may be done (see p. 2001); this procedure, though much less invasive, reduces the recurrence rate to only about 25%.

Viral Pleuritis

Viral pleuritis is a viral infection of the pleurae.

Viral pleuritis is most commonly caused by infection with coxsackie B virus. Occasionally, echovirus causes a rare condition known as epidemic or Bornholm's pleurodynia, manifesting as pleuritis, fever, and chest muscle spasms. The condition occurs in the late summer and affects adolescents and young adults.

The primary symptom of viral pleuritis is pleuritic pain; pleural friction rub may be a sign (see p. 1998).

Diagnosis is suspected in patients with pleuritic chest pain with or without systemic symptoms of viral infection. Chest x-ray is usually done. Other causes of pleuritic chest pain, such as pulmonary emboli and pneumonia, need to be considered and sometimes ruled out with testing.

Treatment is symptomatic, with oral NSAIDs or a short course of oral opioids if needed.

Chapter 205. Tumors of the Lungs

Introduction

Lung tumors may be primary or metastatic from other sites in the body. Primary tumors of the lung may be malignant (see Table 205-1) or benign (see Table 205-2). The most common lung tumor is lung carcinoma, also called bronchogenic carcinoma or lung cancer.

Lung Carcinoma

Lung carcinoma is the leading cause of cancer-related death worldwide. About 85% of cases are related to cigarette smoking. Symptoms can include cough, chest discomfort or pain, weight loss, and, less commonly, hemoptysis; however, many patients present with metastatic disease without any clinical symptoms. The diagnosis is typically made by chest x-ray or CT scan and

[**Table 205-1.** Classification of Primary Malignant Lung Tumors]

confirmed by biopsy. Depending on the stage of the disease, treatment includes surgery, chemotherapy, radiation therapy, or a combination. Despite advances in treatment, the prognosis remains poor, with only 15% of patients surviving > 5 yr from time of diagnosis. For patients with stage IV (metastatic) disease, the 5-yr overall survival rate is < 1%. Improving survival requires focusing attention on smoking cessation, early detection, and research into the genetic profile of lung tumors and developing novel forms of therapy.

Epidemiology

In 2007, an estimated 213,380 new cases of lung cancer were diagnosed in the US, and about 160,390 people died from the disease. The incidence of lung cancer has been rising in women but appears to be leveling off in men.

Etiology

Cigarette smoking is the most important cause of lung cancer, accounting for about 85% of cases. The risk of cancer differs by age, smoking intensity, and smoking duration; the risk of cancer declines after smoking cessation, but it never returns to baseline. About 15% of people who develop lung cancer have never smoked. In these people, the exact reason lung cancer develops is unknown. Recent studies have reported that some never-smoking people with lung cancer have genetic mutations in the epidermal growth factor gene (*EGFR*). Although an environmental association has not clearly been established, it is theorized that exposure to radon gas, a breakdown product of naturally occurring radium and uranium, may be an environmental risk factor. Other possible risk factors include exposure to secondhand smoke and exposure to carcinogens, such as asbestos, radiation, arsenic, chromates, nickel, chloromethyl ethers, mustard gas, or coke-oven emissions, encountered or breathed in at work.

The risk of lung cancer increases with combined exposure to occupational carcinogens, toxins, and cigarette smoking. It is suspected that COPD and pulmonary fibrosis (α_1-antitrypsin deficiency) may increase susceptibility to lung cancer. Also, active smokers who take β-carotene supplements have an increased risk of developing lung cancer. Air pollution and cigar smoke contain carcinogens; these substances have not been shown to cause lung cancer, although they may be associated with an increased risk. People whose lungs are scarred by other lung diseases (eg, TB) are at an increased risk of lung cancer.

Respiratory epithelial cells require prolonged exposure to cancer-promoting agents and accumulation of multiple genetic mutations before becoming neoplastic (an effect called field carcinogenesis). Over time, mutations in genes that stimulate cell growth (*K-ras, MYC*) cause abnormalities in growth factor receptor signaling (*EGFR, HER2/neu*), inhibit apoptosis (*BCL-2*), and contribute to proliferation of abnormal cells.

In addition, mutations that inhibit tumor-suppressor genes (*p53, APC*) can lead to cancer.

[**Table 205-2.** Classification of Benign Lung Tumors]

Classification

Lung cancer is classified into 2 major categories:

• Small cell lung cancer (SCLC)

• Non-small cell lung cancer (NSCLC)

SCLC is highly aggressive and almost always occurs in smokers. It is rapidly growing, and roughly 60% of patients have widespread metastatic disease at the time of diagnosis.

The clinical behavior of NSCLC is more variable and depends on histologic type, but about 40% of patients have metastatic disease outside of the chest at the time of diagnosis.

Other features of the 2 categories (eg, location, risks, treatment, complications) also vary (see Table 205-3).

Symptoms and Signs

About 25% of lung cancers are asymptomatic and are detected incidentally with chest imaging. Symptoms and signs can result from local tumor progression, regional spread, or distant metastases. Paraneoplastic syndromes and constitutional symptoms may occur at any stage of the disease. Although symptoms are not specific to the classification or histology of the cancer, certain complications may be more likely with different types (see Table 205-3).

Local tumor: The local tumor can cause cough and, less commonly, dyspnea due to airway obstruction, postobstructive atelectasis, and lymphangitic spread. Fever may occur with postobstructive pneumonia. Up to half of patients report vague or localized chest pain. Hemoptysis is less common, and blood loss is minimal, except in rare instances when the tumor erodes into a major artery, causing massive hemorrhage and death by exsanguination and asphyxiation.

Regional spread: Regional spread of the tumor may cause pleuritic chest pain or dyspnea

[**Table 205-3.** Features of Lung Cancer]

due to development of a pleural effusion, hoarseness due to tumor encroachment on the recurrent laryngeal nerve, and dyspnea and hypoxia caused by diaphragmatic paralysis due to involvement of the phrenic nerve.

Superior vena cava (SVC) syndrome results from compression or invasion of the SVC and can cause headache or a sensation of head fullness, facial or upper-extremity swelling, supine breathlessness, and flushing (plethora). Physical signs of SVC syndrome include facial and upper-extremity edema, dilated neck and subcutaneous veins in the face and upper trunk, and facial and truncal plethora.

Apical tumors, usually NSCLC, can invade the brachial plexus, pleura, or ribs, causing shoulder and upper-extremity pain and weakness or atrophy of the ipsilateral hand (Pancoast's tumor). Horner's syndrome (ptosis, miosis, enophthalmos, and anhidrosis) results when the paravertebral sympathetic chain or cervical stellate ganglion is involved. Spread of the tumor to the pericardium may be asymptomatic or lead to constrictive pericarditis or cardiac tamponade (see p. 2201). Rarely, esophageal compression causes dysphagia.

Metastases: Metastases eventually cause symptoms that vary by location. Metastases to the liver cause pain, GI symptoms, and ultimately hepatic insufficiency. Metastases to the brain cause behavioral changes, confusion, aphasia, seizures, paresis or paralysis, nausea and vomiting, and ultimately coma

and death. Bone metastases can lead to severe pain and pathologic fractures. Although lung cancer commonly metastasizes to the adrenal glands, it rarely leads to adrenal insufficiency.

Paraneoplastic syndromes: Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastases (see p. 1054). Common paraneoplastic syndromes in patients with lung cancer include hypercalcemia (in patients with squamous cell carcinoma, which results because the tumor produces parathyroid hormone-related protein), syndrome of inappropriate antidiuretic hormone secretion (SIADH), finger clubbing with or without hypertrophic pulmonary osteoarthropathy, hypercoagulability with migratory superficial thrombophlebitis (Trousseau's syndrome), myasthenia (Eaton-Lambert syndrome), and various neurologic syndromes, including neuropathies, encephalopathies, encephalitides, myelopathies, and cerebellar disease. Mechanisms for neuromuscular syndromes involve tumor expression of autoantigens with production of autoantibodies, but the cause of most other syndromes is unknown.

Diagnosis

• Chest x-ray

• CT or combined PET-CT

• Cytopathology examination of pleural fluid or sputum

• Usually bronchoscopy-guided biopsy and fine-needle aspiration

• Sometimes open lung biopsy

Chest x-ray is often the initial imaging test. It may show clearly defined abnormalities, such as a single mass or multifocal masses or a solitary pulmonary nodule (see p. 1841), an enlarged hilum, widened mediastinum, tracheobronchial narrowing, atelectasis, nonresolving parenchymal infiltrates, cavitary lesions, or unexplained pleural thickening or effusion. These findings are suggestive but not diagnostic of lung cancer and require follow-up with CT or combined PET-CT and cytopathologic confirmation.

CT demonstrates many characteristic anatomic patterns and appearances that may confirm the diagnosis. CT also can guide needle biopsy of accessible lesions and is useful for staging. If a lesion found on a plain x-ray is highly likely to be lung cancer, PET-CT may be done. This study combines anatomic imaging from CT with functional imaging from PET. The PET images can help differentiate inflammatory and malignant processes.

The method used to obtain cells or tissue for confirmation depends on the accessibility of tissue and the location of lesions. Sputum or pleural fluid cytology is the least invasive method. In patients with productive cough, sputum specimens obtained on awakening may contain high concentrations of malignant cells, but yield for this method is < 50% overall. Pleural fluid is another convenient source of cells; a malignant effusion is a poor prognostic sign (see Table 205-4). In general, false-negative cytology readings can be minimized by obtaining as large a volume of sputum or fluid as possible early in the day and sending the sample to the pathology laboratory immediately to minimize delays in processing, which lead to cell breakdown.

A percutaneous biopsy is the next least invasive procedure. It is more useful for metastatic sites (supraclavicular or other peripheral lymph nodes, pleura, liver, adrenals) than for lung lesions because of the 20 to 25% risk of pneumothorax and the risk of false-negative results.

Bronchoscopy is the procedure most often used for diagnosing lung cancer. In theory, the procedure of choice for obtaining tissue is the one that is least invasive. In practice, bronchoscopy is often done in addition to or instead of less invasive procedures because diagnostic yields are greater and because bronchoscopy is important for staging. A combination of washings, brushings, biopsies, and fine-needle aspirations of visible endobronchial lesions and of paratracheal, subcarinal, mediastinal, and hilar lymph nodes often yields a tissue diagnosis.

Mediastinoscopy is the gold standard test for evaluating mediastinal lymph nodes but is a higher-risk procedure, which is usually used before surgery to confirm or exclude the presence of tumor in enlarged mediastinal lymph nodes.

Open lung biopsy, done via open thoracotomy or using video assistance (see p. 1865), is indicated when less invasive methods do not provide a diagnosis in patients whose clinical characteristics and radiographic features strongly suggest that the tumor is resectable.

Screening: No screening studies are universally accepted for healthy patients who do not have lung cancer. Clinical trials have evaluated screening chest x-rays in high-risk patients (smokers) to try to detect lung cancers at earlier stages, but mortality did not decline. Screening CT is being evaluated because it is more sensitive, but CT produces more false-positive results, which increase the number of unnecessary invasive diagnostic procedures needed to verify the CT findings. Such procedures are costly and risk additional complications. A strategy of yearly CT screening of smokers with follow-up PET or high-resolution CT (HRCT) to evaluate indeterminate lesions is currently being studied. So far, this strategy does not seem to lessen mortality and cannot be recommended as routine practice. The future of screening may lie in a combination of molecular analysis for genetic markers (eg, *K-ras*, *p53*, *EGFR*), sputum cytometry, and detection of cancer-related volatile organic compounds (eg, alkane, benzene) in exhaled breath.

[**Table 205-4.** Proposed International Staging System for Lung Cancer*]

Staging

SCLC has 2 stages: limited and extensive. Limited-stage SCLC is cancer confined to one hemithorax (including ipsilateral lymph nodes) that can be encompassed within one tolerable radiation therapy port, unless there is a pleural or pericardial effusion. Extensive-stage disease is cancer outside a single hemithorax or the presence of malignant cells detected in pleural or pericardial effusions. Less than one third of patients with SCLC present with limited-stage disease; the remainder of patients often have extensive distant metastases.

NSCLC has 4 stages: I through IV. Staging is based on tumor size, tumor and lymph node location, and the presence or absence of distant metastases (see Table 205-4).

Tests for initial evaluation and staging: All lung cancer patients need whole-body imaging. Different combinations of tests can be done. Some tests are done routinely, and others are done depending on whether the results would affect treatment decisions:

• PET or integrated PET-CT

• CT from neck to pelvis (done if PET-CT is not available)

• MRI of chest (for tumors near apex or diaphragm to evaluate vascular supply)

• Biopsy of questionable nodes (if PET is indeterminate)

• Bone scan (done with CT if PET-CT is not available)

• Head CT or brain MRI

Measurement of serum Ca and alkaline phosphatase; evaluation of liver function, immune system, and kidney function; platelets; Hb; and electrolytes are needed to assist with treatment decisions.

If PET-CT is not available, thin-section CT scanning from the neck to the upper abdomen (to detect cervical and supraclavicular and hepatic and adrenal metastases) is one of the first staging tests for both SCLC and NSCLC. However, CT often cannot distinguish postinflammatory changes from malignant intrathoracic lymph node enlargement or benign lesions from malignant hepatic or adrenal lesions (distinctions that determine stage). Thus, other tests are usually done when abnormalities are present in

these areas. PET is a reasonably accurate, noninvasive test used to identify malignant mediastinal lymph nodes and other distant metastases (metabolic staging). Integrated PET-CT, in which PET and CT images are combined into a single image by scanners in a single gantry, is more accurate for NSCLC staging than CT or PET alone or than visual correlation of the 2 tests. The use of PET and integrated PET-CT is limited by cost, availability, and specificity (ie, the test is quite sensitive and has an excellent negative predictive value, but its positive predictive value is not as high). When PET results are indeterminate, bronchoscopy, mediastinoscopy, or video-assisted thoracoscopic surgery (VATS) can be used to biopsy questionable mediastinal lymph nodes. Without PET, hepatic or adrenal lesions must be evaluated by needle biopsy.

MRI of the chest is slightly more accurate than high-chest HRCT for staging apical tumors and cancers close to the diaphragm and provides evaluation of the vasculature surrounding the tumors.

Blood tests are usually done. Ca and alkaline phosphatase levels, if elevated, suggest possible bone metastases. Other blood tests, such as CBC, serum albumin levels, AST, ALT, total bilirubin, electrolytes, and creatinine levels, have no role in staging but provide important prognostic information about the patient's ability to tolerate treatment and may detect paraneoplastic syndromes.

All patients with suspected lung cancer should undergo brain imaging. Brain imaging is especially necessary in patients with headache or neurologic abnormalities. Patients with bone pain or elevated serum Ca or alkaline phosphatase levels should undergo a PET-CT or radionuclide bone scanning if PET-CT is not available.

Prognosis

The overall prognosis for lung cancer is poor. The median survival time for limited-stage SCLC is 20 mo, with a 5-yr survival rate of 20%. Patients with extensive-stage SCLC do especially poorly, with a 5-yr survival rate of < 1%.

The 5-yr survival rate of patients with NSCLC varies by stage, from 60 to 70% for patients with stage I disease to < 1% for patients with stage IV disease. On average, untreated patients with metastatic NSCLC survive 6 mo, whereas the median survival for treated patients is about 9 mo. Recently, patient survival has improved in both early and later stage NSCLC. Evidence shows improved survival in early-stage disease when platinum-based chemotherapy regimens are used after surgical resection. In addition, targeted therapies have improved survival in patients with stage IV disease. However, given the disappointing results in patients with metastatic disease, efforts at reducing mortality have increasingly focused on early detection and active interventions to prevent disease. Basing therapy on molecular signatures within the tumors has been the focus of laboratory and translational research.

Treatment

• Surgery (depending on cell type and stage)

• Chemotherapy

• Radiation therapy

Treatment varies by cell type and by stage of disease. Many patient factors not related to the tumor affect treatment choice. Poor cardiopulmonary reserve, undernutrition, frailty or poor physical performance status, comorbidities (including cytopenias), and psychiatric or cognitive illness all may lead to a decision for palliative rather than curative treatment or for no treatment at all, even though a cure with aggressive therapy might technically be possible.

Radiation therapy has the risk of radiation pneumonitis when large areas of the lung are exposed to high doses of radiation over time. Radiation pneumonitis can occur up to 3 mo after treatment is completed. Cough, dyspnea, low-grade fever, or pleuritic chest pain may signal the condition, as may crackles or a pleural friction rub detected during chest auscultation. Chest x-ray findings may be nonspecific; CT may show a nonspecific infiltrate without an obvious mass. The diagnosis is often one of exclusion. Radiation

pneumonitis can be treated with a corticosteroid taper over several weeks and bronchodilators for symptom relief.

Multiple chemotherapy regimens exist for treatment of lung cancer. In addition to standard chemotherapy drugs, several biologic agents that specifically target lung tumors are under investigation. EGFR tyrosine kinase inhibitors may be used in patients who have not responded to platinum-based or docetaxel therapy. Bevacizumab, a vascular endothelial growth factor inhibitor, is now used in combination with standard chemotherapy regimens in certain patients. Many other biologic agents are under investigation; some specifically target cancer cell signal transduction pathways or the angiogenesis pathways that supply O_2 and nutrition to growing tumor cells.

Radiofrequency ablation, in which high-frequency electrical current is used to destroy tumor cells, is a newer technique that can sometimes be used in patients who have small, early-stage tumors or small tumors that have recurred in a previously irradiated chest. This procedure may preserve more lung function than open surgery does and, because it is less invasive, may be appropriate for patients who are not candidates for open surgery.

SCLC: Typically, SCLC of any stage is initially responsive to treatment, but responses are usually short-lived. Chemotherapy, with or without radiation therapy, is given depending on the stage of disease. In many patients, chemotherapy prolongs survival and improves quality of life enough to warrant its use. Surgery generally plays no role in treatment of SCLC, although it may be curative in the rare patient who has a small focal tumor without spread (such as a solitary pulmonary nodule) and who had surgical resection before the tumor was identified as SCLC.

Chemotherapy regimens of etoposide and a platinum compound (either cisplatin or carboplatin) are commonly used, as are other drugs, such as irinotecan, topotecan, vinca alkaloids (vinblastine, vincristine, vinorelbine), alkylating agents (cyclophosphamide, ifosfamide), doxorubicin, taxanes (docetaxel, paclitaxel), and gemcitabine. In limited-stage disease, radiation therapy further improves response; the very definition of limited-stage disease as disease confined to a hemithorax is based on the significant improvement in survival observed with radiation therapy. The use of cranial radiation to prevent brain metastases is also advocated in certain cases of limited- and extensive-stage disease; micrometastases are common in SCLC, and chemotherapy has less ability to cross the blood-brain barrier.

In extensive-stage disease, treatment is based on chemotherapy rather than radiation therapy, although radiation therapy is often used as palliative treatment for metastases to bone or brain. In patients with an excellent response to chemotherapy, prophylactic brain irradiation is sometimes used, as in limited-stage SCLC to prevent growth of SCLC in the brain. It is unclear whether replacing etoposide with topoisomerase inhibitors (irinotecan or topotecan) improves survival. These drugs alone or in combination with other drugs are also commonly used in refractory disease and in cancer of either stage that has recurred.

In general, patients with recurrent SCLC have a poor prognosis, although patients who maintain a good performance status should be offered a clinical trial.

NSCLC: Treatment for NSCLC typically involves assessment of eligibility for surgery followed by choice of surgery, chemotherapy, radiation therapy, or a combination of modalities as appropriate, depending on tumor type and stage.

For stage I and II disease, the standard approach is surgical resection with either lobectomy or pneumonectomy combined with mediastinal lymph node sampling or complete lymph node dissection. Lesser resections, including segmentectomy and wedge resection, are considered for patients with poor pulmonary reserve. Surgery is curative in about 55 to 75% of patients with stage I and in 35 to 55% of patients with stage II disease.

Surgery is done only if NSCLC patients will have adequate pulmonary reserve once a lobe or lung is resected. Patients with preoperative forced expiratory volume in 1 sec (FEV_1) > 2 L generally tolerate

pneumonectomy. Those with FEV_1 < 2 L should have a quantitative xenon radionuclide perfusion scan to determine the proportion of function the patient can expect to lose from resection. Postoperative FEV_1 can be predicted by multiplying percent perfusion of the nonresected lung by the preoperative FEV_1. A predicted FEV_1 > 800 mL or > 40% of the predicted normal FEV_1 suggests adequate postoperative lung function, although studies of lung volume reduction surgery in COPD patients suggest that patients with FEV_1 < 800 mL can tolerate resection if the cancer is located in poorly functional, bullous (generally apical) lung regions. Patients undergoing resection at hospitals that do more resections have fewer complications and are more likely to survive than those who undergo surgery at hospitals that do fewer lung cancer procedures.

Adjuvant chemotherapy after surgery is now standard practice for patients with stage II or stage III disease, possibly also for patients with stage IB disease with tumors > 4 cm. Clinical trials have shown an increase in 5-yr survival rates with the use of adjuvant chemotherapy. However, the decision for adjuvant chemotherapy should depend on the patient's comorbidities and risk assessment. The role of neoadjuvant chemotherapy in early-stage NSCLC is under investigation.

Stage III disease is treated with either chemotherapy, radiation therapy, surgery, or a combination; the sequence and choice of treatment depend on the location of the patient's disease and comorbidities. In general, concurrent chemotherapy and radiation therapy are considered standard treatment for unresectable clinically staged IIIA disease, but survival remains poor (median survival, 10 to 14 mo). Patients with stage IIIB disease plus contralateral mediastinal nodal disease or supraclavicular nodal disease are offered either radiation therapy or chemotherapy or both. Patients with locally advanced tumors invading the heart, great vessels, mediastinum, or spine usually receive radiation therapy. In some patients (with T4 N0 M0 tumors), surgical resection with either neoadjuvant or adjuvant combined chemotherapy and radiation therapy may be feasible. The 5-yr survival rate for patients with treated stage IIIB disease is 5%.

In stage IV disease, palliation of symptoms is the goal. Chemotherapy and radiation therapy may be used to reduce tumor burden, treat symptoms, and improve quality of life. However, median survival is only 9 mo, and < 25% of patients survive 1 yr. Surgical palliative procedures may be required and may include thoracentesis and pleurodesis of recurrent effusions, placement of indwelling pleural drainage catheters, bronchoscopic fulguration of tumors involving the trachea and mainstem bronchi, placement of stents to prevent airway occlusion, and, in some cases, spinal stabilization for impending spinal cord compression.

Recurrent disease: Treatment options for disease that recurs after treatment vary by location and include repeat chemotherapy for local recurrence, radiation therapy for metastases, and brachytherapy for endobronchial disease when additional external radiation cannot be tolerated. Rarely, surgical resection of a solitary metastasis or for palliative purposes is considered. The treatment of a locally recurrent NSCLC follows the same guidelines as for primary tumor stages I to III. If surgery was used initially, radiation therapy is the main modality. If the recurrence manifests as distant metastases, patients are treated as stage IV with a focus on palliation.

Complications: Asymptomatic malignant pleural effusions require no treatment. Initial treatment of a symptomatic effusion is with thoracentesis; symptomatic effusions that recur despite multiple thoracenteses are drained through a chest tube. Infusion of talc (or occasionally, tetracycline or bleomycin) into the pleural space (a procedure called pleurodesis) scars the pleura, eliminates the pleural space, and is effective in > 90% of cases (see p. 1995).

Treatment of SVC syndrome is the same as treatment of lung cancer, with chemotherapy (SCLC), radiation therapy (NSCLC), or both (NSCLC). Corticosteroids are commonly used but are of unproven benefit.

Treatment of Horner's syndrome caused by apical tumors is with surgery with or without preoperative radiation or with radiation therapy with or without adjuvant chemotherapy.

Treatment of paraneoplastic syndromes varies by syndrome (see p. 1054).

End-of-life care: Because many patients with lung cancer die, the need for end-of-life care should be anticipated (see p. 3480). Symptoms of breathlessness can be treated with supplemental oxygen and bronchodilators. Pain, anxiety, nausea, and anorexia are especially common and can be treated with parenteral morphine; oral, transdermal, or parenteral opioids; and antiemetics. The care provided by hospice programs is extremely well-accepted by patients and families, yet this intervention is markedly underused.

Prevention

No active interventions to prevent lung cancer have proved to be effective except for smoking cessation (see p. 3432). Remediation of high radon levels in private residences removes known cancer-promoting radiation, but a reduction in lung cancer incidence is unproved. Increasing dietary intake of fruits and vegetables high in retinoids and β-carotene appears to have no effect on lung cancer incidence. Vitamin supplementation is either unproved (vitamin E) or harmful (β-carotene) in smokers. Preliminary evidence hinting that NSAIDs and vitamin E supplementation may protect former smokers from lung cancer requires confirmation. New molecular approaches targeting cell signaling and cell cycle pathways and tumor-associated antigens are under investigation.

Airway Tumors

The airway can be affected by primary tracheobronchial tumors, primary tumors that are adjacent to and invade the airway, or cancers that metastasize to the airway.

Primary tracheal tumors are rare (0.1/100,000 people). They are often malignant and found at a locally advanced stage. The most common malignant tracheal tumors include adenoid cystic carcinoma, squamous cell carcinoma, carcinoid, and mucoepidermoid carcinomas. The most common benign airway tumor is a squamous papilloma, although pleomorphic adenomas and granular cell and benign cartilaginous tumors also occur.

Symptoms and Signs

Patients often present with dyspnea, cough, wheezing, hemoptysis, and stridor. Hemoptysis may occur with a squamous cell carcinoma and can potentially lead to earlier diagnosis, whereas wheezing or stridor occurs more often with the adenoid cystic variant. Dysphagia and hoarseness can also be present initially and usually indicate advanced disease.

Diagnosis

• Bronchoscopic biopsy

Symptoms of airway narrowing can herald life-threatening airway obstruction and require immediate hospitalization and evaluation with bronchoscopy. Bronchoscopy can both stabilize the airways and allow specimens to be obtained for diagnosis. If cancer is found, more extensive testing for metastases is done (see p. 2007).

Prognosis

Prognosis depends on the histology. Squamous cell carcinomas tend to metastasize to regional lymph nodes and directly invade mediastinal structures, leading to high local and regional recurrence rates. Even with definitive surgical resection, the 5-yr survival is only 20 to 40%. Adenoid cystic carcinomas are typically indolent but tend to metastasize to the lungs and to spread perineurally, leading to high recurrence rates after resection. However, these patients have a higher 5-yr survival of 60 to 75% because of the slow rate of growth.

Treatment

• Surgery

• Sometimes radiation therapy

• Obstruction reduction techniques

Primary airway tumors should be treated definitively with surgical resection if possible. Tracheal, laryngotracheal, or carinal resections are the most common procedures. Up to 50% of the length of the trachea can be safely resected with primary re-anastomosis. If a lung or thyroid cancer invades the airway, surgery is sometimes still feasible if assessment indicates sufficient tissue is available for airway reconstruction. Adjuvant radiation therapy is recommended if adequate surgical margins cannot be obtained.

Most primary airway tumors are not resectable because of metastasis, locally advanced stage, or patient comorbidities. In cases of endoluminal tumors, a therapeutic bronchoscopy can mechanically core-out the tumor. Other techniques to eliminate obstruction include laser vaporization, photodynamic therapy, cryotherapy, and endobronchial brachytherapy. Tumors that compress the trachea are treated with airway stenting, radiation therapy, or both.

Bronchial Carcinoid

Bronchial carcinoids are rare, slow-growing neuroendocrine tumors arising from bronchial mucosa; they affect patients in their 40s to 60s.

Half of patients are asymptomatic, and half present with symptoms of airway obstruction, including dyspnea, wheezing, and cough, which often leads to a misdiagnosis of asthma. Recurrent pneumonia, hemoptysis, and chest pain are also common. Paraneoplastic syndromes, including Cushing's syndrome due to ectopic ACTH, acromegaly due to ectopic growth hormone-releasing factor, and Zollinger-Ellison syndrome due to ectopic gastrin production, are more common than carcinoid syndrome (see p. 908), which occurs in < 3% of patients with the tumor. A left-sided heart murmur (mitral stenosis or regurgitation) occurs rarely due to serotonin-induced valvular damage (as opposed to the right-sided valvular lesions of GI carcinoid).

Diagnosis is based on bronchoscopic biopsy, but evaluation often initially involves chest CT, which reveals tumor calcifications in up to one third of patients. Indium-111-labeled octreotide scans are useful for determining regional and metastatic spread. Increased urinary serotonin and 5-hydroxyindoleacetic acid levels support the diagnosis, but these substances are not commonly elevated.

Treatment is with surgical removal with or without adjuvant therapy. Prognosis depends on tumor type. Five-year survival for typical (well-differentiated) carcinoids is > 90%; for atypical tumors, it is 50 to 70%.

Chest Wall Tumors

Chest wall tumors are benign or malignant tumors that can interfere with pulmonary function.

Primary chest wall tumors account for 5% of all thoracic tumors and 1 to 2% of all primary tumors. Almost half are benign; the most common are osteochondroma, chondroma, and fibrous dysplasia. A wide range of malignant chest wall tumors exist. Over half are metastases from distant organs or direct invasions from adjacent structures (breast, lung, pleura, mediastinum). The most common malignant primary tumors arising from the chest wall are sarcomas; about 45% originate from soft tissue, and 55% from cartilaginous or bone tissue. Chondrosarcomas are the most common primary bone chest wall sarcoma and arise in the anterior tract of ribs and less commonly from the sternum, scapula, or clavicle. Other bone tumors include osteosarcoma and small-cell malignant tumors (Ewing's sarcoma, Askin's tumor). The most common soft-tissue primary malignant tumors are fibrosarcomas (desmoids, neurofibrosarcomas) and malignant fibrous histiocytomas. Other primary tumors include chondroblastomas, osteoblastomas, melanomas, lymphomas, rhabdomyosarcomas, lymphangiosarcomas, multiple myeloma, and plasmacytomas.

Symptoms and Signs

Soft-tissue chest wall tumors often manifest as a localized mass without other symptoms. Some patients have fever. Patients usually do not experience pain until the tumor is more advanced. In contrast, primary cartilaginous and bone tumors are often painful.

Diagnosis

Patients with chest wall tumors require chest x-ray, CT, MRI, and sometimes PET-CT to determine the original site and extent of the tumor and its status (primary chest wall tumor or a metastasis). Biopsy and histologic evaluation confirm the diagnosis.

Prognosis

Prognosis varies by cancer type, cell differentiation, and stage; firm conclusions are limited by the low incidence of any given tumor. Sarcomas have been the most well studied, and primary chest wall sarcomas have a reported 5-yr survival of 17%. Survival is better with early-stage disease.

Treatment

• Surgery

• Sometimes combination chemotherapy, radiation therapy, and surgery

Most chest wall tumors are treated with surgical resection and reconstruction. Reconstruction often uses a combination of myocutaneous flaps and prosthetic materials. The presence of a malignant pleural effusion is a contraindication for surgical resection. Also, in cases of multiple myeloma or isolated plasmacytoma, chemotherapy and radiation should be the primary therapy. Small-cell malignant tumors such as Ewing's sarcoma and Askin's tumor should be treated with a multimodality approach combining chemotherapy, radiation therapy, and surgery. In cases of chest wall metastasis from distant tumors, a palliative chest wall resection is recommended only when nonsurgical options do not alleviate symptoms.