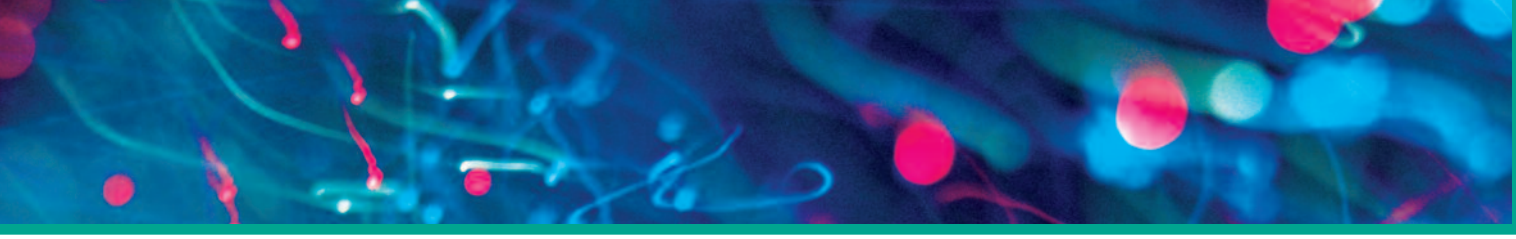

Chapter 21

Respiratory Tract Infections, Neoplasia, and Childhood Disorders

Respiratory illnesses represent one of the more common reasons for visits to the physician, admission to the hospital, and forced inactivity among all age groups. The common cold, although not usually serious, results in missed work and school days. Pneumonia is the sixth leading cause of death in the United States, particularly among the elderly and those with compromised immune function. Tuberculosis remains one of the deadliest diseases in the world. In addition to microbial pathogens, cigarette smoking contributes significantly to disorders of the respiratory tract, including lung cancer. The content in this chapter is divided into three sections: respiratory tract infections, cancer of the lung, and respiratory disorders in children.

Respiratory Tract Infections

Respiratory tract infections can involve the upper respiratory tract (*i.e.*, nose, oropharynx, and larynx), the lower respiratory tract (*i.e.*, lower airways and lungs), or the upper and lower airways. The discussion in this section of the chapter focuses on the common cold, rhinosinusitis, influenza, pneumonia, tuberculosis, and fungal infections of the lung. Acute respiratory infections in children are discussed in the last section of the chapter.

The respiratory tract is susceptible to infectious processes caused by many different types of microorganisms. For the most part, the signs and symptoms of respiratory tract infections depend on the function of the structure involved, the severity of the infectious process, and the person's age and general health status.

Viruses are the most frequent cause of respiratory tract infections. They can cause infections ranging from a self-limited cold to life-threatening pneumonia. Moreover, viral infections can damage bronchial epithelium, obstruct

airways, and lead to secondary bacterial infections. Each viral species has its own pattern of respiratory tract involvement. The rhinoviruses grow best at 33°C to 35°C and remain strictly confined to the upper respiratory tract.[1] The influenza viruses can infect both the upper and lower respiratory tracts. Measles and chickenpox viruses "pass through" the respiratory tract and do not cause respiratory symptoms until secondary viremic spread has occurred. Other microorganisms, such as bacteria (*e.g.,* pneumococci, staphylococci), mycobacteria (*e.g., Mycobacterium tuberculosis*), fungi (*e.g.,* histoplasmosis, coccidioidomycosis, blastomycosis), and opportunistic organisms (*e.g., Pneumocystis carinii*), also produce infections of the lung, many of which produce significant morbidity and mortality.

THE COMMON COLD

The common cold is a viral infection of the upper respiratory tract. It occurs more frequently than any other respiratory tract infection. Most adults have two to four colds per year; the average school child may have up to 10 per year.[2] The condition usually begins with a feeling of dryness and stuffiness affecting mainly the nasopharynx; it is accompanied by excessive production of nasal secretions and lacrimation, or tearing of the eyes. Usually, the secretions remain clear and watery. The mucous membranes of the upper respiratory tract become reddened, swollen, and bathed in secretions. Involvement of the pharynx and larynx causes sore throat and hoarseness. The affected person may experience headache and generalized malaise. In severe cases, there may be chills, fever, and exhaustion. The disease process is usually self-limited, lasting approximately 7 days.

Initially thought to be caused by either a single "cold virus" or a group of them, the common cold is now recognized to be associated with a number of viruses.[3] The most common of these are the rhinoviruses, parainfluenza viruses, respiratory syncytial virus, coronaviruses, and adenoviruses. The season of the year, age, and prior exposure are important factors in the type of virus causing the infection and the type of symptoms that occurs. For example, outbreaks of colds due to the rhinoviruses are most common in early fall and late spring; those due to the respiratory syncytial virus peak in the winter and spring months; and infections due to the adenoviruses and coronaviruses are more frequent during the winter and spring months. Infections resulting from the respiratory syncytial virus and parainfluenza viruses are most common and severe in children younger than 3 years of age. The rhinoviruses are the most common cause of colds in persons between 5 and 40 years of age. There are over 100 serotypes of rhinovirus.[3,4] Although people acquire lifetime immunity to an individual serotype, it would take a long time to become immune to all serotypes.

The "cold viruses" are rapidly spread from person to person. Children are the major reservoir of cold viruses, often acquiring a new virus from another child in school or day care. The fingers are the greatest source of spread, and the nasal mucosa and conjunctival surface of the eyes are the most common portals of entry of the virus. The most highly contagious period is during the first 3 days after the onset of symptoms, and the incubation period is approximately 5 days. Cold viruses have been found to survive for more than 5 hours on the skin and hard surfaces, such as plastic countertops.[3,4] Aerosol spread of colds through coughing and sneezing is much less important than the spread by fingers picking up the virus from contaminated surfaces and carrying it to the nasal membranes and eyes.[5] This suggests that careful attention to hand washing is one of the most important preventive measures for avoiding the common cold.

Because the common cold is an acute and self-limited illness in persons who are otherwise healthy, symptomatic treatment with rest and antipyretic drugs is usually all that is needed. Antibiotics are ineffective against viral infections and are not recommended. Efforts to develop vaccines against the cold viruses have been largely unsuccessful, mainly because of the number of viruses involved and their large array of serotypes.

RHINOSINUSITIS

The term *rhinosinusitis* is a more accurate term for what is commonly called *sinusitis,* because the mucous membranes of the nose and paranasal sinuses are contiguous and subject to the same conditions.[6] The paranasal sinuses are air-filled extensions of the respiratory part of the nasal cavities into the frontal, ethmoid, sphenoid, and maxilla bones (Fig. 21-1). The sinuses, which are named for the bones in which they are found, are connected by narrow openings or *ostia* with the superior, middle, and inferior nasal turbinates of the nasal cavity.[6,7] The mucosal lining of the paranasal sinuses, like that of the nasal passages, has numerous ciliated and columnar cells whose cilia help move fluid and microorganisms out of the sinuses and into the nasal cavity. The lower oxygen content in the sinuses facilitates the growth of organisms, impairs local defenses, and alters the function of immune cells.

The most common causes of rhinosinusitis are conditions that obstruct the narrow ostia that drain the sinuses. Most commonly, rhinosinusitis develops when upper respiratory tract infection or allergic rhinitis (discussed in Chapter 15) narrows the ostia and obstructs the flow of mucus. Nasal polyps also can obstruct the sinus opening and facilitate sinus infection. Barotrauma caused by changes in barometric pressure, as occurs in airline pilots and flight attendants, may lead to impaired sinus ventilation and clearance of secretions. Swimming, diving, and abuse of nasal decongestants are other causes of sinus irritation and impaired drainage.

Clinical Features

Rhinosinusitis can be classified as acute, subacute, or chronic.[6–8] Acute rhinosinusitis may be of viral, bacterial, or mixed viral-bacterial origin and may last from 5 to 7 days in the case of acute viral rhinosinusitis and up to 4 weeks in the case of acute bacterial rhinosinusitis. Recurrent acute rhinosinusitis is defined as four or more

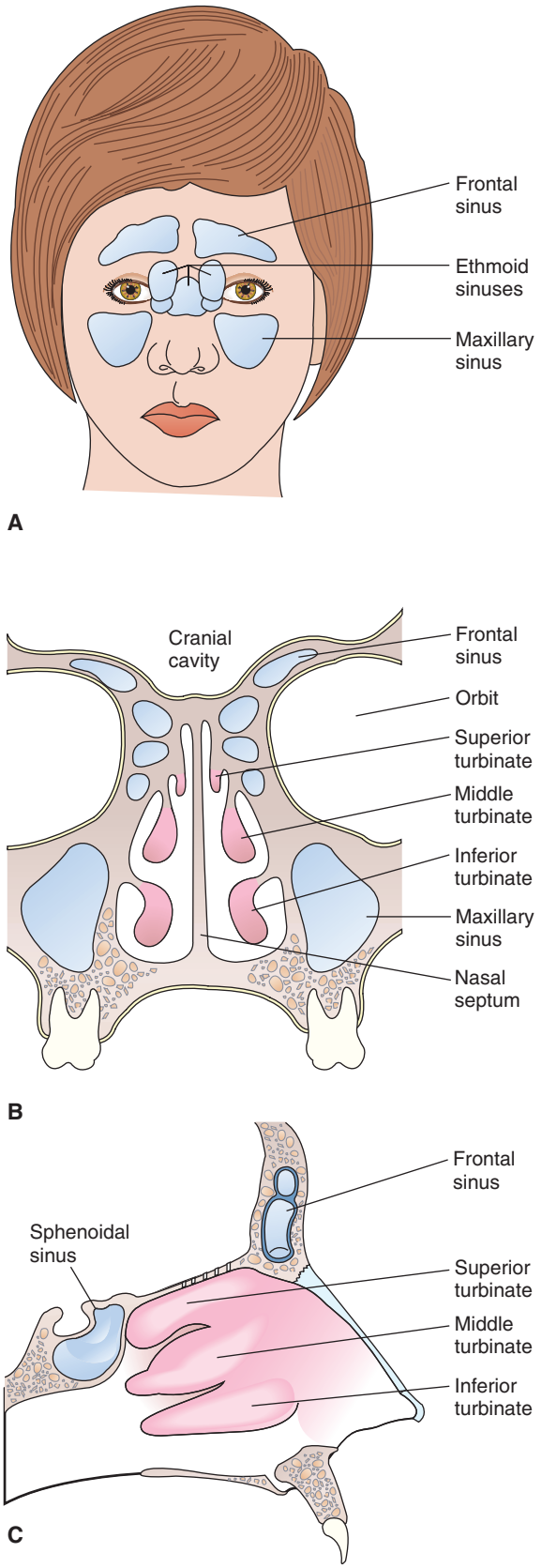

FIGURE 21-1 Paranasal sinuses. (**A**) Frontal view; (**B**) cross section of nasal cavity, anterior view; (**C**) lateral wall, left nasal cavity. (Courtesy of Carole Russell Hilmer, C.M.I.)

episodes of acute disease within a 12-month period. Subacute rhinosinusitis lasts from 4 weeks to less than 12 weeks, whereas chronic rhinosinusitis lasts beyond 12 weeks.

Acute bacterial rhinosinusitis most commonly results from infection with *Haemophilus influenzae* or *Streptococcus pneumoniae*.[6–8] In chronic rhinosinusitis, anaerobic organisms, including species of *Peptostreptococcus, Fusobacterium,* and *Prevotella,* tend to predominate, alone or in combination with aerobes such as the *Streptococcus* species or *Staphylococcus aureus*. In immunocompromised persons, such as those with human immunodeficiency virus (HIV) infection, the sinuses may become infected with gram-negative species and opportunistic fungi. In this group, particularly those with leukopenia, the disease may have a fulminant and even fatal course.

Potential complications of bacterial sinusitis include local extension to the sinus bones, infection of the intracranial cavity, and the spread of infection to the central nervous system, resulting in meningitis or brain abscess.

Manifestations. The symptoms of acute rhinosinusitis often are difficult to differentiate from those of the common cold and allergic rhinitis. They include facial pain, headache, purulent nasal discharge, decreased sense of smell, and fever. A history of a preceding common cold and the presence of purulent rhinitis, pain on bending, unilateral maxillary pain, and pain in the teeth are common findings with involvement of the maxillary sinuses. The symptoms of acute viral rhinosinusitis usually resolve within 5 to 7 days without medical treatment. Acute bacterial rhinosinusitis is suggested by symptoms that worsen after 5 to 7 days or persist beyond 10 days, or symptoms that are out of proportion to those usually associated with a viral upper respiratory tract infection.[9]

In persons with chronic rhinosinusitis, the only symptoms may be those such as nasal obstruction, a sense of fullness in the ears, postnasal drip, hoarseness, chronic cough, loss of taste and smell, or unpleasant breath. Sinus pain often is absent; instead, the person may complain of a headache that is dull and constant. Persons with chronic rhinosinusitis may have superimposed bouts of acute rhinosinusitis. The epithelial changes that occur during acute and subacute forms of rhinosinusitis usually are reversible, but the mucosal changes that occur with chronic rhinosinusitis often are irreversible.

Diagnosis and Treatment. The diagnosis of rhinosinusitis usually is based on symptom history and a physical examination that includes inspection of the nose and throat. Headache due to sinusitis needs to be differentiated from other types of headache. Sinusitis headache usually is exaggerated by bending forward, coughing, or sneezing. Physical examination findings in acute bacterial sinusitis include turbinate edema, nasal crusts, purulence of the nasal cavity, and failure of transillumination of the maxillary sinuses. Transillumination is done in a completely darkened room by placing a flashlight against the skin overlying the infraorbital rim, directing the light inferiorly, having the person open his or her mouth, and observing the hard palate for light transmission.[9] Sinus

radiographs and computed tomography (CT) scans may be used. CT scans usually are reserved for diagnosis of chronic rhinosinusitis or to exclude complications.

Treatment of rhinosinusitis includes appropriate antibiotic therapy. The duration of antibiotic therapy is longer for chronic rhinosinusitis than for acute rhinosinusitis. In addition to antibiotic therapy, the treatment of acute rhinosinusitis includes measures to promote adequate drainage by reducing nasal congestion. Oral and topical decongestants may be used for this purpose. The use of intranasal decongestants should be limited to 3 to 5 days to prevent rebound vasodilatation.[8] The use of antihistamines is controversial, particularly for acute rhinosinusitis, because they can dry up secretions and thereby decrease drainage. Mucolytic agents such as guaifenesin may be used to thin secretions. Topical corticosteroids may be used to decrease inflammation in persons with allergic rhinitis or rhinosinusitis. Nonpharmacologic measures include saline nasal sprays and steam inhalations.

Surgical intervention directed at correcting obstruction of the ostiomeatal openings may be indicated in persons with chronic rhinosinusitis that is resistant to other forms of therapy. Indications for surgical intervention include obstructive nasal polyps and obstructive nasal deformities.

INFLUENZA

Influenza is a viral infection that can affect the upper and lower respiratory tracts. Until the advent of acquired immunodeficiency syndrome (AIDS), it was the last uncontrolled pandemic killer of humans. In the United States, approximately 36,000 persons die each year of influenza-related illness during nonpandemic years.[10] Rates of infection are highest among children, but rates of serious illness and death are highest among persons who are 65 years of age or older.

There are three types of influenza viruses that cause disease in humans: types A, B, and C. Type A affects humans, pigs, horses, and birds and is the major cause of epidemics and pandemics. The influenza viruses are further divided into subtypes based on two surface glycoproteins: hemagglutinin (HA) and neuroaminidase (NA).[10,11] Hemagglutinin is an attachment protein that allows the virus to enter epithelial cells in the respiratory tract, and NA facilitates viral replication and release from the cell. Host antibodies to HA or NA prevent or ameliorate infection with the influenza virus. Contagion results from the ability of the influenza A virus to develop new HA and NA subtypes (e.g., H1, H2, H3, N1, N2, N3) against which the population is not protected. An *antigenic shift,* which involves a major change in either antigen, may lead to epidemic or pandemic infection. Influenza B and C viruses do not exhibit antigenic shift, probably because few related viruses exist in animals.

As with many viral respiratory tract infections, influenza is more contagious than bacterial respiratory tract infections. Transmission is by aerosol or direct contact. Inhalation of as few as three infective particles can transmit the infection.[12] Young children are most likely to become infected and also to spread the infection. The incubation period for influenza is 1 to 4 days, with 2 days being the average. Persons become infectious starting 1 day before their symptoms begin and remain infectious through approximately 5 days after illness onset.[10] Children can be infectious for greater than 10 days, and young children can shed virus for up to 6 days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months.

Pathogenesis

The influenza viruses can cause three types of infections: an uncomplicated upper respiratory infection (rhinotracheitis), viral pneumonia, and a respiratory viral infection followed by a bacterial infection. Influenza initially establishes upper airway infection. In doing this, the virus first targets and kills mucous-secreting, ciliated, and other epithelial cells, leaving gaping holes between the underlying basal cells and allowing extracellular fluid to escape. This is the reason for the "runny nose" that is characteristic of this phase of the infection. If the virus spreads to the lower respiratory tract, the infection can cause severe shedding of bronchial and alveolar cells down to a single-cell–thick basal layer. In addition to compromising the natural defenses of the respiratory tract, influenza infection promotes bacterial adhesion to epithelial cells. Pneumonia may result from a viral pathogenesis or from a secondary bacterial infection.

Clinical Features

In the early stages, the symptoms of influenza often are indistinguishable from other viral infections. There is an abrupt onset of fever and chills, malaise, muscle aching, headache, profuse, watery nasal discharge, nonproductive cough, and sore throat.[10,13] One distinguishing feature of influenza is the rapid onset, sometimes within minutes, of profound malaise. The symptoms of uncomplicated rhinotracheitis usually peak by days 3 to 5 and disappear by days 7 to 10. The symptoms above can be caused by any strain of influenza A or B. Influenza C causes symptoms similar to those of the common cold.

Viral pneumonia occurs as a complication of influenza most frequently in the elderly or in persons with cardiopulmonary disease, but has been reported in pregnant women and in healthy, immunocompetent people. It typically develops within 1 day after onset of symptoms and is characterized by rapid progression of fever, tachypnea, tachycardia, cyanosis, and hypotension.[14,15] The clinical course of influenza pneumonia progresses rapidly. It can cause hypoxemia and death within a few days of onset. Survivors often develop diffuse pulmonary fibrosis.[15]

Secondary complications typically include sinusitis, otitis media, bronchitis, and bacterial pneumonia. Reye syndrome (fatty liver with encephalitis) is a rare complication of influenza, particularly in young children.[15] It is most commonly associated with aspirin use during a viral infection such as influenza. Persons who develop secondary bacterial pneumonia usually report that they were beginning to feel better when they experienced a return of fever, shaking chills, pleuritic chest pain, and productive cough. The most common causes of secondary bacterial pneu-

monia are *S. pneumoniae, S. aureus, H. influenzae,* and *Moraxella catarrhalis*. Influenza-related deaths, particularly in the elderly, can result from pneumonia as well as exacerbations of cardiopulmonary conditions and other disease.

Diagnosis and Treatment. The appropriate treatment of people with influenza depends on accurate and timely diagnosis. Early diagnosis can reduce the inappropriate use of antibiotics and provide the opportunity for use of an antiviral drug. Rapid diagnostic tests, which are available for use in outpatient settings, allow health care providers to diagnose influenza more accurately, consider treatment options more carefully, and monitor influenza type and its prevalence in their community.[16]

The goals of treatment for influenza are designed to limit the infection to the upper respiratory tract. The symptomatic approach for treatment of uncomplicated influenza rhinotracheitis focuses on rest, keeping warm, and drinking large amounts of liquids. Antipyretic and cough medications can also be used. Rest decreases the oxygen requirements of the body and reduces the respiratory rate and the chance of spreading the virus from the upper to lower respiratory tract. Keeping warm helps maintain the respiratory epithelium at a core body temperature of 37°C (or higher if fever is present), thereby inhibiting viral replication, which is optimal at 35°C. Drinking large amounts of liquids ensures that the function of the epithelial lining of the respiratory tract is not further compromised by dehydration. Antiviral medications may be indicated in some persons. Antibacterial antibiotics should be reserved for bacterial complications. The use of aspirin to treat fever should be avoided in children.

Four antiviral drugs are available for treatment of influenza: amantadine, rimantadine, zanamivir, and oseltamivir.[17,18] The first-generation antiviral drugs amantadine and rimantadine are similarly effective against influenza A but not influenza B. These agents inhibit the uncoating of viral ribonucleic acid (RNA) in the host cells and prevent its replication. Both drugs are effective in prevention of influenza A in high-risk groups and in treatment of persons who acquire the disease. Unfortunately, resistance to the drugs develops rapidly and strains that are resistant to amantadine also are resistant to rimantadine. The second-generation antiviral drugs zanamivir and oseltamivir are inhibitors of NA, the viral glycoprotein that is necessary for viral replication and release. These drugs, which result in less resistance than amantadine and rimantadine, have been approved for treatment of acute uncomplicated influenza infection and are effective against both influenza A and B viruses. Zanamivir is administered intranasally and oseltamivir is administered orally. Zanamivir can cause bronchospasm and is not recommended for persons with asthma or chronic obstructive lung disease. To be effective, the antiviral drugs should be initiated within 30 hours after onset of symptoms.

Influenza Immunization

Because influenza is so highly contagious, prevention relies primarily on immunization.[19] Currently, there are two types of influenza vaccines available: the trivalent inactivated influenza vaccine (TIIV), which was developed in the 1940s, and the live, attenuated influenza vaccine (LAIV), which was approved for use in 2003.[20] The formulation of the vaccines must be changed yearly in response to antigenic changes in the influenza virus. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) annually updates its recommendations for the composition of the vaccine.

The TIIV, which is administered by injection, has become the mainstay for prevention of influenza. It has proven to be inexpensive and effective in reducing illness caused by influenza.

Immunization is recommended for members of high-risk groups who, because of their age or underlying health problems, are unable to cope well with the infection and often require medical attention, including hospitalization. Immunization is also recommended for persons who can transmit the infection to high-risk groups (*e.g.,* health care workers and caregivers). Because the TIIV is an inactivated vaccine, it is thought to be safe during pregnancy.[10] The effectiveness of the influenza vaccine in preventing and lessening the effects of influenza infection depend primarily on the age and immunocompetence of the recipient and the match between the virus strains included in the vaccine and those that circulate during the influenza season.[10,19] When there is a good match, the vaccine is effective in preventing the illness in approximately 70% to 90% of healthy persons younger than 65 years of age.[10,19]

The LAIV, which is administered intranasally, has been approved for use in healthy persons 5 to 49 years of age.[20] The LAIVs are in use in Russia and have been in development in the United States since the 1960s. The LAIVs are cold-adapted viruses that replicate efficiently in the 25°C temperature of the nasopharynx, inducing protective immunity against viruses included in the vaccine, but replicate inefficiently at the 38°C to 39°C temperature of the lower airways.

PNEUMONIAS

The term *pneumonia* describes inflammation of parenchymal structures of the lung, such as the alveoli and the bronchioles. Although antibiotics have significantly reduced the mortality rate from pneumonias, these diseases remain the sixth leading cause of death in the United States and are an important immediate cause of death in the elderly and persons with debilitating diseases.[21] Etiologic agents include infectious and noninfectious agents. Although much less common than infectious pneumonia, inhalation of irritating fumes or aspiration of gastric contents can result in severe pneumonia.

Classification

Pneumonias can be classified according the type of agent (typical or atypical) causing the infection, distribution of the infection (lobar pneumonia or bronchopneumonia), and setting (community or hospital) in which it occurs.

KEY CONCEPTS

Pneumonias

- Pneumonias are respiratory disorders involving inflammation of the lung structures, such as the alveoli and bronchioles.
- Pneumonia can be caused by infectious agents, such as bacteria and viruses, and noninfectious agents, such as gastric secretions that are aspirated into the lungs.
- The development of pneumonia is facilitated by an exceedingly virulent organism, large inoculum, and impaired host defenses.
- Pneumonias caused by infectious agents commonly are classified according to the source of infection (community- vs. hospital-acquired) and according to the immune status of the host (pneumonia in the immunocompromised person).

Typical pneumonias result from infection by bacteria that multiply extracellularly in the alveoli and cause inflammation and exudation of fluid into the air-filled spaces of the alveoli (Fig. 21-2). *Atypical pneumonias* are caused by viral and mycoplasma infections that involve the alveolar septum and interstitium of the lung. They produce less striking symptoms and physical findings than bacterial pneumonia; there is a lack of alveolar infiltration and purulent sputum, leukocytosis, and lobar consolidation on the radiograph.[21] Acute bacterial pneumonias can be classified as lobar pneumonia or bronchopneumonia, based on their anatomic pattern of distribution.[22] In general, *lobar pneumonia* refers to consolidation of a part or all of a lung lobe, and *bronchopneumonia* signifies a patchy consolidation involving more than one lobe (Fig. 21-3).

Because of the overlap in symptomatology and changing spectrum of infectious organisms involved, pneumonias are increasingly being classified according to the setting (community-acquired or hospital-acquired) in which they occur. Persons with compromised immune function constitute a special concern in both categories.

Community-Acquired Pneumonia. The term *community-acquired pneumonia* is used to describe infections from organisms found in the community rather than in the hospital or nursing home. It is defined as an infection that begins outside the hospital or is diagnosed within 48 hours after admission to the hospital in a person who has not resided in a long-term care facility for 14 days or more before admission.[23] Community-acquired pneumonia may be further categorized according to risk of mortality and need for hospitalization based on age, presence of coexisting disease, and severity of illness as determined by physical examination, laboratory, and radiologic findings.[24]

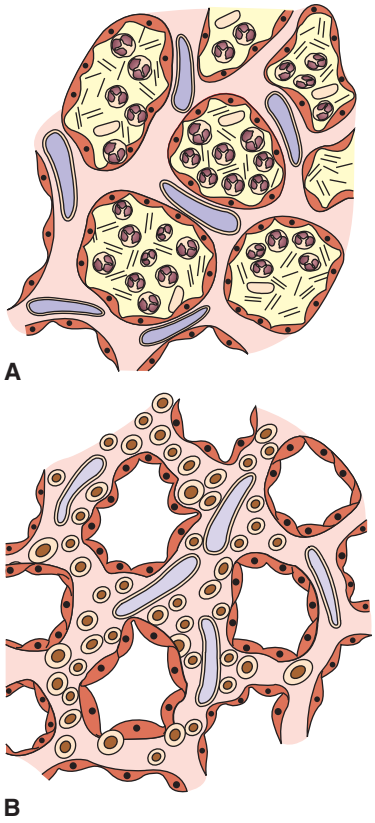

FIGURE 21-2 Location of inflammatory processes in (**A**) typical and (**B**) atypical forms of pneumonia.

Community-acquired pneumonias may be either bacterial or viral. The most common cause of community-acquired pneumonia is *S. pneumoniae*.[21] Other common pathogens include *H. influenzae*, *S. aureus*, and gram-negative bacilli. Less common agents are *M. catarrhalis*,

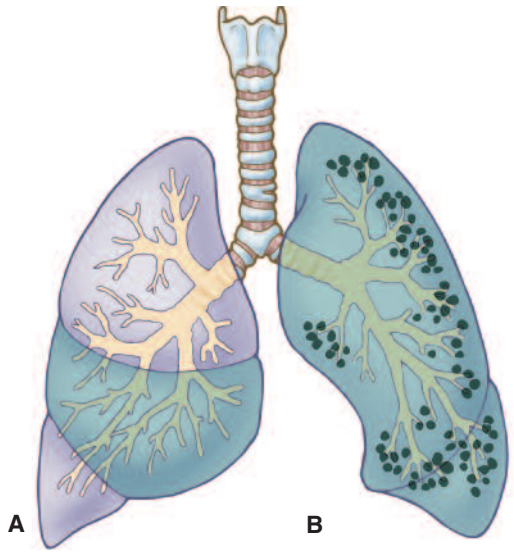

FIGURE 21-3 Distribution of lung involvement in (**A**) lobar pneumonia and (**B**) bronchopneumonia.

Klebsiella pneumoniae, and *Neisseria meningitidis*. *Legionella* species, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* (strain TWAR), sometimes called *atypical agents,* account for 20% to 40% of all cases.[25] Common viral causes of community-acquired pneumonia include the influenza virus, respiratory syncytial virus, adenovirus, and parainfluenza virus.

The methods used in the diagnosis of community-acquired pneumonia depend on age, coexisting health problems, and the severity of illness. In persons younger than 65 years of age and without coexisting disease, the diagnosis usually is based on history and physical examination, chest radiographs, and knowledge of the microorganisms currently causing infections in the community. Sputum specimens may be obtained for staining procedures and culture. Blood cultures may be done for persons requiring hospitalization.

Hospital-Acquired Pneumonia. Hospital-acquired, or nosocomial, pneumonia is defined as a lower respiratory tract infection that was not present or incubating on admission to the hospital. Usually, infections occurring 48 hours or more after admission are considered hospital acquired.[23,26] Hospital-acquired pneumonia is the second most common cause of hospital-acquired infection and has a mortality rate of 20% to 50%.[26] Persons requiring mechanical ventilation are particularly at risk, as are those with compromised immune function, chronic lung disease, and airway instrumentation, such as endotracheal intubation or tracheotomy.

Ninety percent of infections are bacterial. The organisms are those present in the hospital environment and include *Pseudomonas aeruginosa, S. aureus, Enterobacter* species, *Klebsiella* species, *Escherichia coli,* and *Serratia*. The organisms that are responsible for hospital-acquired pneumonias are different from those responsible for community-acquired pneumonia, and many of them have acquired antibiotic resistance and are more difficult to treat.

Pneumonia in Immunocompromised Persons. Pneumonia in immunocompromised persons remains a major source of morbidity and mortality. The term *immunocompromised host* usually is applied to persons with a variety of underlying defects in host defenses. It includes persons with primary and acquired immunodeficiency states, those who have undergone bone marrow or organ transplantation, persons with solid organ or hematologic cancers, and those on corticosteroid and other immunosuppressant drugs.[27]

Although almost all types of microorganisms can cause pulmonary infection in immunocompromised persons, certain types of immunologic defects tend to favor certain types of infections. Defects in humoral immunity predispose to bacterial infections against which antibodies play an important role; defects in cellular immunity predispose to infections with viruses, fungi, mycobacteria, and protozoa. Neutropenia and impaired granulocyte function, as occur with leukemia, chemotherapy, and bone marrow metaplasia, predispose to infections caused by *S. aureus, Aspergillus,* gram-negative bacilli, and *Candida*. The time course of infection often provides a hint to the type of agent involved. A fulminant pneumonia usually is caused by bacterial infection, but an insidious onset probably heralds viral, fungal, protozoal, or mycobacterial infection.

Acute Bacterial (Typical) Pneumonias

Bacterial pneumonias remain an important cause of morbidity and mortality, particularly among the elderly. Most bacteria that cause bacterial pneumonia are normal inhabitants of the oropharynx or nasopharynx and reach the alveoli by aspiration of secretions. Other routes of infection include inhalation of microorganisms in the environment. Normally, these organisms do not cause infection because of the small number that are inhaled or aspirated and because the respiratory tract's defense mechanisms prevent them from entering the distal airways[21] (Table 21-1). Loss of the cough reflex, damage to the ciliated endothelium that lines the respiratory tract, and impaired immune defenses predispose to colonization and infection of the lower respiratory system. Bacterial adherence also plays a role in colonization of the lower airways. The epithelial cells of critically and chronically ill persons are more receptive to binding microorganisms that cause pneumonia. Other clinical risk factors favoring colonization of

TABLE 21-1 Respiratory Defense Mechanisms and Conditions That Impair Their Effectiveness

Defense Mechanism	Function	Factors That Impair Effectiveness
Glottic and cough reflexes	Protect against aspiration into tracheobronchial tree	Loss of cough reflex due to stroke or neural lesion, neuromuscular disease, abdominal or chest surgery, depression of the cough reflex due to sedation or anesthesia, presence of a nasogastric tube (tends to cause adaptation of afferent receptors)
Mucociliary blanket	Removes secretions, microorganisms, and particles from the respiratory tract	Smoking, viral diseases, chilling, inhalation of irritating gases
Phagocytic and bactericidal action of alveolar macrophages	Removes microorganisms and foreign particles from the lung	Tobacco smoke, chilling, alcohol, oxygen intoxication
Immune defenses (IgA and IgG and cell-mediated immunity)	Destroys microorganisms	Congenital and acquired immunodeficiency states

the tracheobronchial tree include antibiotic therapy that alters the normal bacterial flora, diabetes, smoking, chronic bronchitis, and viral infection.

Bacterial pneumonias are usually classified according to etiologic agent. This is because the clinical and morphologic features, and thus the therapeutic implications, often vary with the causative agent. The discussion in this section focuses on two types of bacterial pneumonia: *S. pneumoniae* pneumonia and Legionnaires disease.

S. pneumoniae Pneumonia. *S. pneumoniae* (pneumococcus) remains the most common cause of bacterial pneumonia. *S. pneumoniae* are gram-positive diplococci, possessing a capsule of polysaccharide. There are 90 serologically distinct types of *S. pneumoniae* based on the antigenic properties of their capsular polysaccharides. The virulence of the pneumococcus is a function of its capsule, which prevents or delays digestion by phagocytes. The polysaccharide is an antigen that primarily elicits a B-cell response with antibody production. In the absence of antibody, clearance of the pneumococci from the body relies on the reticuloendothelial system, with the macrophages in the spleen playing a major role in elimination of the organism.[28] This, along with the spleen's role in antibody production, increases the risk of pneumococcal bacteremia in persons who are anatomically or functionally asplenic, such as children with sickle cell disease. The initial step in the pathogenesis of pneumococcal infection is the attachment and colonization of the organism in the nasopharynx. Colonization does not equate with signs of infection. Perfectly healthy people can be colonized without evidence of infection; the spread of particular strains of pneumococci, particularly antibiotic-resistant strains, is largely by healthy colonized individuals.

The signs and symptoms of pneumococcal pneumonia vary widely, depending on the age and health of the infected person. In previously healthy persons, the onset usually is sudden and is characterized by malaise, severe shaking chill, and fever. The temperature may go as high as 106°F. During the initial or congestive stage, coughing brings up watery sputum, and breath sounds are limited, with fine crackles. As the disease progresses, the character of the sputum changes; it may be blood tinged or rust colored to purulent. Pleuritic pain, a sharp pain that is more severe with respiratory movements, is common. With antibiotic therapy, fever usually subsides in approximately 48 to 72 hours, and recovery is uneventful. Elderly persons are less likely to experience marked elevations in temperature; in these persons, the only sign of pneumonia may be a loss of appetite and deterioration in mental status.

Treatment includes the use of antibiotics that are effective against *S. pneumoniae*. In the past, *S. pneumoniae* was uniformly susceptible to penicillin. However, penicillin-resistant and multidrug-resistant strains have been emerging in the United States and other countries.[24,25,28]

Pneumococcal pneumonia can be prevented through immunization. A 23-valent pneumococcal vaccine, composed of antigens from 23 types of *S. pneumoniae* capsular polysaccharides, is used.[29] The vaccine is recommended for persons 65 years of age or older and persons aged 2 to 65 years with chronic illnesses, immunocompromised persons 2 years of age or older, for residents in special environments or social settings in which the risk for invasive pneumococcal disease is increased, and for residents of nursing homes and long-term care facilities. Because their immune system is immature, the antibody response to most pneumococcal capsular polysaccharides usually is poor or inconsistent in children younger than 2 years of age. A 7-valent pneumococcal polysaccharide-protein conjugate vaccine (Prevnar) is now available for use in infants and children.[30]

Legionnaires Disease. Legionnaires disease is a form of bronchopneumonia caused by a gram-negative rod, *Legionella pneumophila*. It ranks among the three or four most common causes of community-acquired pneumonia.[31] The organism frequently is found in water, particularly in warm, standing water. Although healthy persons can contract the infection, the risk is greatest among smokers, persons with chronic diseases, and those with impaired cell-mediated immunity.[21]

Symptoms of the disease typically begin approximately 2 to 10 days after infection, with malaise, weakness, lethargy, fever, and dry cough. Other manifestations include disturbances of central nervous system function, gastrointestinal tract involvement, arthralgias, and elevation in body temperature, sometimes to more than 104°F. The presence of pneumonia along with diarrhea, hyponatremia, and confusion is characteristic of *Legionella* pneumonia. The disease causes consolidation of lung tissues and impairs gas exchange.

Diagnosis is based on clinical manifestations, radiologic studies, and specialized laboratory tests to detect the presence of the organism. Of these, the *Legionella* urinary antigen test is a relatively inexpensive, rapid test that detects antigens of *L. pneumophila* in the urine.[31] The urine test usually is easier to obtain because people with legionellosis often have a nonproductive cough and the results remain positive for weeks despite antibiotic therapy.

Treatment consists of administration of antibiotics that are known to be effective against *L. pneumophila*. Delay in instituting antibiotic therapy significantly increases mortality rates; therefore, antibiotics known to be effective against *L. pneumophila* should be included in the treatment regimen for severe community-acquired pneumonia.

Primary Atypical Pneumonias

The primary atypical pneumonias are characterized by patchy inflammatory changes in the lungs, largely confined to the alveolar septa and pulmonary interstitium. The term *atypical pneumonia* denotes a lack of lung consolidation, production of moderate amounts of sputum, moderate elevation of white blood cell count, and lack of alveolar exudate.[22] These pneumonias are caused by a variety of agents, the most common being *Mycoplasma pneumoniae*. Mycoplasma infections are particularly common among children and young adults. Other etiologic agents include viruses (*e.g.*, influenza virus, respiratory syncytial viruses, adenoviruses, rhinoviruses, and the rubeola [measles] and varicella [chickenpox] viruses) and *Chlamydia pneumoniae*. In some cases, the cause is unknown.

The clinical course among persons with atypical pneumonias varies widely from a mild infection that masquerades as a chest cold to a more serious and even fatal outcome (*e.g.*, chickenpox pneumonia). The symptoms may remain confined to chills and fever, headache, and muscle aches and pains. Cough, when present, is characteristically dry, hacking, and nonproductive. The diagnosis is usually made based on history, physical findings, and chest radiographs.

The sporadic form of atypical pneumonia is usually mild with a low mortality rate. It may, however, assume epidemic proportions with intensified severity and greater mortality as in the influenza pandemics of 1915 and 1918. The agents that cause atypical pneumonias damage the respiratory tract epithelium and impair respiratory tract defenses, thereby predisposing to secondary bacterial infections.

TUBERCULOSIS

Pulmonary tuberculosis is the world's foremost cause of death from a single infectious agent, causing 26% of avoidable deaths in developing countries.[32,33] It is more common among foreign-born persons from countries with a high incidence of tuberculosis and among residents of high-risk congregate settings such as correctional facilities, drug treatment facilities, and homeless shelters. There is increased occurrence of tuberculosis among HIV-positive individuals. Worldwide, it is one of the leading causes of morbidity and mortality among people with HIV infection. Outbreaks of a drug-resistant form of tuberculosis have occurred, complicating the selection of drugs and affecting the duration of treatment.

Tuberculosis is an infectious disease caused by the mycobacterium, *M. tuberculosis hominis* (human tuberculosis). The mycobacteria are slender, rod-shaped, aerobic bacteria that do not form spores. They are similar to other bacterial organisms except for an outer waxy capsule that makes them more resistant to destruction; the organism can persist in old necrotic and calcified lesions and remain capable of reinitiating growth. The waxy coat also causes the organism to retain red dye when treated with acid in acid-fast staining.[33,34] Thus, the mycobacteria are often referred to as *acid-fast bacilli.* Although *M. tuberculosis* can infect practically any organ of the body, the lungs are most frequently involved.

Tuberculosis is an airborne infection spread by minute, invisible particles called *droplet nuclei* that are harbored in the respiratory secretions of persons with active tuberculosis. Coughing, sneezing, and talking all create respiratory droplets; these droplets evaporate, leaving the organisms (droplet nuclei), which remain suspended in the air and are circulated by air currents. Thus, living under crowded and confined conditions increases the risk for spread of the disease.

KEY CONCEPTS

Tuberculosis

- Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis,* a rod-shaped aerobic bacterium that is resistant to destruction and can persist in necrotic and calcified lesions for prolonged periods and remain capable of reinstating growth.
- The organism is spread by inhaling the mycobacterium-containing droplet nuclei that circulate in the air.
- The cell-mediated response plays a dominant role in walling off the tubercle bacilli and preventing the development of active tuberculosis. People with impaired cell-mediated immunity are more likely to experience active tuberculosis when infected.
- A positive tuberculin skin test results from a cell-mediated immune response and implies that a person has been infected with *M. tuberculosis* and has mounted a cell-mediated immune response. It does not mean that the person has active tuberculosis.

Pathogenesis

The pathogenesis of tuberculosis in a previously unexposed immunocompetent person is centered on the development of a cell-mediated immune response that confers resistance to the organism and development of hypersensitivity to the tubercular antigens[33,34] (see Chapter 15). The pathologic manifestations of tuberculosis, such as caseating granuloma and cavitation, are the result of the hypersensitivity reaction that the bacillus evokes, rather than its inherent destructive capabilities.

Macrophages are the primary cell infected with *M. tuberculosis*. Inhaled droplet nuclei pass down the bronchial tree without settling on the epithelium and are deposited in the alveoli. Soon after entering the lung, the bacilli are surrounded and engulfed by macrophages. Although the macrophages that first ingest *M. tuberculosis* cannot kill the organisms, they initiate a cell-mediated immune response that eventually contains the infection. As the tubercle bacilli multiply, the infected macrophages degrade the mycobacteria and present their antigens to T lymphocytes. The sensitized T lymphocytes, in turn, stimulate the macrophages to increase their concentration of lytic enzymes and ability to kill the mycobacteria. When released, these lytic enzymes also damage lung tissue. The development of a population of activated T lymphocytes and the related development of activated macrophages capable of ingesting and destroying the bacilli constitute the cell-mediated immune response, a process that takes about 3 to 6 weeks to become effective.

In persons with intact cell-mediated immunity, the cell-mediated immune response results in the development of a gray-white, circumscribed granulomatous lesion, called a *Ghon focus,* that contains the tubercle bacilli, modified macrophages, and other immune cells.[34] It is usually located in the subpleural area of the upper segments of

the lower lobes or in the lower segments of the upper lobe. When the number of organisms is high, the hypersensitivity reaction produces significant tissue necrosis, causing the central portion of the Ghon focus to undergo soft, caseous (cheeselike) necrosis. During this same period, tubercle bacilli, free or inside macrophages, drain along the lymph channels to the tracheobronchial lymph nodes of the affected lung and there evoke the formation of caseous granulomas. The combination of the primary lung lesion and lymph node granulomas is called *Ghon complex* (Fig. 21-4).

Primary Tuberculosis

Primary tuberculosis is a form of the disease that develops in previously unexposed, and therefore unsensitized persons. It typically is initiated as a result of inhaling droplet nuclei that contain the tubercle bacillus[33,34] (Fig. 21-5). Primary tuberculosis usually is clinically and radiologically silent. Most people with primary tuberculosis go on to develop *latent infection* in which T lymphocytes and macrophages surround the organism in granulomas that limit their spread. Individuals with latent tuberculosis do not have active disease and cannot transmit the organism to others.[35]

In approximately 5% of newly infected people, the immune response is inadequate; these people go on to develop progressive primary tuberculosis with continued destruction of lung tissue and spread to multiple sites in the lung.[33] People with HIV infection and others with disorders of cell-mediated immunity are more likely to develop progressive tuberculosis if they become infected. In those who develop progressive disease, the symptoms are usually insidious and nonspecific, with fever, weight loss, fatigue, and night sweats. Sometimes the onset of symptoms is abrupt, with high fever, pleuritis, and lymphadenitis. As the disease spreads, the organism gains access to the sputum, allowing the person to infect others.

In rare instances, tuberculosis may erode into a blood vessel, giving rise to hematogenic dissemination. *Miliary tuberculosis* describes minute lesions, resembling millet seeds, resulting from this type of dissemination that can involve almost any organ, particularly the brain, meninges, liver, kidney, and bone marrow.

FIGURE 21-4 Primary tuberculosis. A healed Ghon complex is represented by a subpleural nodule and involved hilar lymph nodes. (From Travis W. D., Beasley M. B., Rubin E. [2005]. The respiratory system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 597]. Philadelphia: Lippincott Williams & Wilkins.)

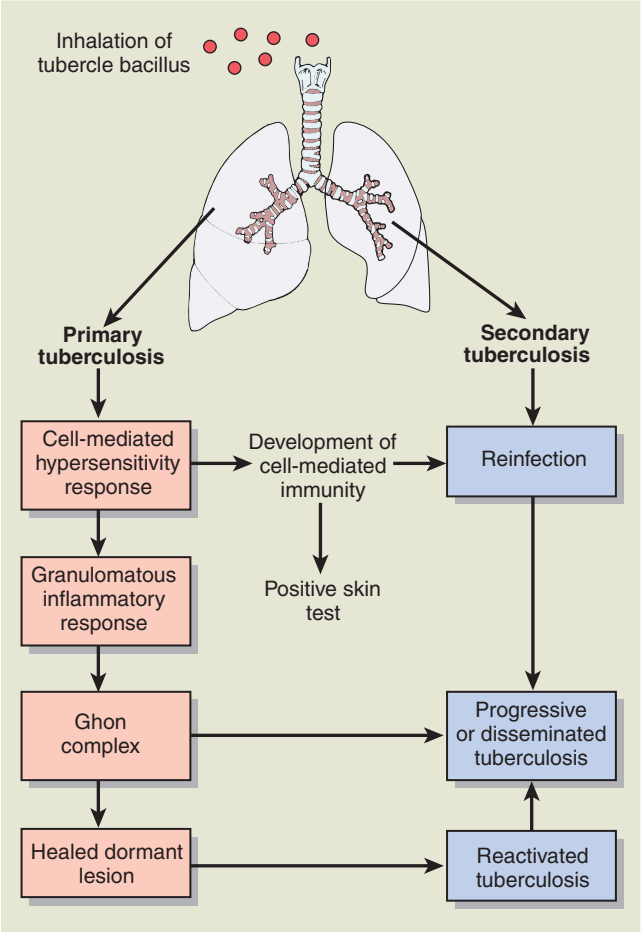

FIGURE 21-5 Pathogenesis of tuberculosis infection.

Secondary Tuberculosis

Secondary tuberculosis represents either reinfection from inhaled droplet nuclei or reactivation of a previously healed primary lesion (see Fig. 21-5). It often occurs in situations of impaired host defenses. Secondary tuberculosis is classically localized in the apex of the upper lobes

of one or both lungs, probably because the higher oxygen content in the apices favors the growth of the bacteria.[33] Because of the preexistence of a cell-mediated immune response, the bacilli elicit a prompt and marked tissue response that tends to wall off the infection. As a result, involvement of the regional lymph nodes is less prominent than in primary tuberculosis. Instead, cavitation occurs readily as the bacteria are disseminated along the airways, and erosion into the airways is a common source of infection. The cavities may coalesce to a size of up to 3 to 10 cm in diameter[34] (Fig. 21-6). Pleural effusion and tuberculous empyema are common as the disease progresses.

Persons with secondary tuberculosis commonly present with cough (which may be erroneously attributed to smoking or a cold), low-grade fevers, night sweats, easy fatigability, anorexia, and weight loss. The cough initially is dry but later becomes productive with purulent and sometimes blood-tinged sputum. Dyspnea and orthopnea develop as the disease advances. Untreated secondary tuberculosis is a wasting disease that is eventually fatal.

Diagnosis and Treatment

Diagnosis. The most frequently used screening methods for pulmonary tuberculosis are the tuberculin skin tests and chest radiographic studies. The tuberculin skin test measures delayed hypersensitivity (*i.e.,* cell-mediated, type IV) that follows exposure to the tubercle bacillus. Persons who become tuberculin positive usually remain so for the remainder of their lives. A positive reaction to the skin test does not mean that a person has active tuberculosis, only that there has been exposure to the bacillus and that cell-mediated immunity to the organism has developed. False-positive and false-negative skin test reactions can occur. False-positive reactions often result from cross-reactions with other mycobacteria, such as *M. avium-intracellulare* complex.[36] Because the hypersensitivity response to the tuberculin test depends on cell-mediated immunity, a false-negative test result can occur because of immunodeficiency states that result from HIV infection, immunosuppressive therapy, lymphoreticular malignancies, or aging. This is called *anergy*. In the immunocompromised person, a negative tuberculin test result can mean that the person has a true lack of exposure to tuberculosis or is unable to mount an immune response to the test. Because of the problem with anergy in persons with HIV infection and other immunocompromised states, the use of control tests is recommended. Three antigens that can be used for control testing are *Candida,* mumps virus, and tetanus toxoid. Most healthy, immunocompetent persons have been exposed to these antigens and will display a positive response to these control tests.[36]

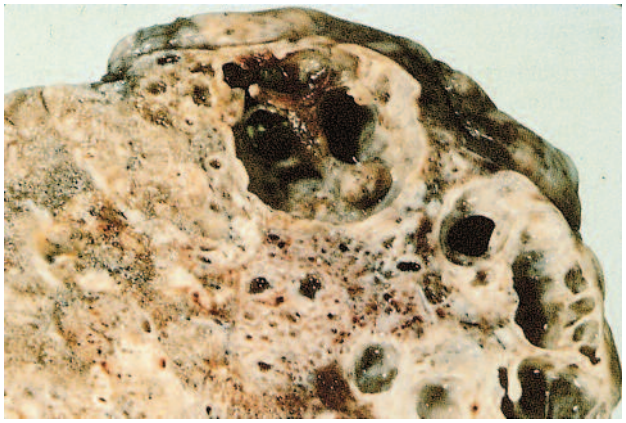

FIGURE 21-6 Cavitary tuberculosis in the apex of the left upper lobe of the lung. (From Travis W. D., Beasley M. B., Rubin E. [2005]. The respiratory system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 598]. Philadelphia: Lippincott Williams & Wilkins.)

A two-step testing procedure, which uses a "boosting" phenomenon, may be used to increase the reaction to a subsequent tuberculin test in persons who have been infected with tuberculosis.[36] If the first test result of the two-step procedure is negative, a second test is administered 1 week later. If the second test result is negative, the person is considered to be uninfected or anergic. If the second test result is positive, it is assumed to have occurred because of a boosted response. The boosted effect can last for 1 year or longer. Use of the two-step test procedure for employee health or institutional screening can reduce the likelihood that a boosted response in a subsequent test will not be interpreted as a recent infection.

Diagnosis of active pulmonary tuberculosis requires identification of the organism in respiratory tract secretions. Bacteriologic studies (*i.e.,* acid-fast stain and cultures) of early sputum specimens, gastric aspirations, or bronchial washings obtained during fiberoptic bronchoscopy may be used. The polymerase chain reaction (PCR) allows rapid detection of *M. tuberculosis* and its differentiation from other mycobacteria (see Chapter 21). Genotyping can be done to identify different strains of *M. tuberculosis*. It can be used to evaluate second episodes of tuberculosis to determine whether the second episode was due to relapse or reinfection. Genotyping also permits the evaluation of isolates with different patterns of drug susceptibility.[37] In addition, genotyping is useful in investigating outbreaks of infection and determining sites and patterns of *M. tuberculosis* transmission in communities.

Treatment. The primary drugs used in the treatment of tuberculosis are isoniazid (INH), rifampin, pyrazinamide, ethambutol, and streptomycin.[38] The tubercle bacillus is an aerobic organism that multiplies slowly and remains relatively dormant in oxygen-poor caseous material. It undergoes a high rate of mutation and tends to acquire resistance to any one drug. For this reason, multidrug regimens are used for treating persons with active tuberculosis.

Two groups meet the criteria established for the use of antimycobacterial therapy for tuberculosis: (1) persons with an active form of the disease, and (2) those who have had contact with cases of active tuberculosis and who are at risk for the development of active tuberculosis. Tuberculosis is an unusual disease in that chemotherapy is required for a relatively long time. Short-course programs

of therapy (usually 6 to 12 months) have replaced the earlier 18- to 24-month multidrug regimens. Treatment may need to be prolonged in persons with HIV infection and in those with drug-resistant strains of *M. tuberculosis*. Drug susceptibility tests are used to guide treatment in drug-resistant forms of the disease.

Outbreaks of multidrug-resistant tuberculosis have posed a problem for the prophylactic treatment of exposed persons, including health care workers.[39] Most exposed persons who have contracted active multidrug-resistant tuberculosis were infected with the HIV virus; the fatality rate among these persons is high. Various treatment protocols are recommended, depending on the type of resistant strain that is identified.

FUNGAL INFECTIONS

Fungal infections are commonly classified as superficial, subcutaneous, deep-seated, and opportunistic pathogenic fungi. The superficial and subcutaneous fungi almost always limit their infections to the skin and subcutaneous tissues. Opportunistic fungi are organisms of low virulence (*e.g., Candida* species) that cause localized or systemic infections in people who are immunocompromised, such as those with HIV infection.

The deep-seated fungal infections are caused by highly virulent dimorphic fungi, with the ability to invade deeply into tissues and cause systemic disease. They include *Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis*. Isolated, self-limited pulmonary involvement is commonly seen in people with normal immune function, whereas immunocompromised people often present with disseminated disease. In HIV-infected persons in endemic areas, coccidioidomycosis is now a common opportunistic infection.

Each of the dimorphic fungi has a typical geographic distribution. *H. capsulatum,* which is the etiologic agent in histoplasmosis, is endemic along the major river valleys of the Midwest—the Ohio, the Mississippi, and the Missouri.[40,41] The organism grows in soil and other areas that have been enriched with bird excreta: old chicken houses, pigeon lofts, barns, and trees where birds roost. The infection is acquired by inhaling the fungal spores that are released when the dirt or dust from the infected areas is disturbed. *C. immitis,* which causes coccidioidomycosis, is most prevalent in the southwestern United States, principally in California, Arizona, and Texas.[42,43] Because of its prevalence in the San Joaquin Valley, the disease is sometimes referred to as *San Joaquin fever* or *valley fever*. *C. immitis* lives in soil and can establish new sites in the soil. Events such as dust storms and digging for construction have been associated with increased incidence of the disease. *B. capsulatum,* the agent causing blastomycosis, is most commonly found in the southern and north central United States, especially in areas bordering the Mississippi and Ohio River basins and the Great Lakes.[44]

Clinical Features

The signs and symptoms of the fungal infections commonly resemble those of tuberculosis. Depending on the host's resistance and immunocompetence, the diseases usually take one of three forms: (1) an acute primary disease, (2) a chronic (cavitary) pulmonary disease, or (3) a disseminated infection. The primary pulmonary lesions consist of nodules containing aggregates of macrophages with engulfed microorganisms. Similar nodules develop in the regional lymph nodes. There is a striking similarity to the primary lesions of tuberculosis. The clinical manifestations consist of a mild, self-limited flulike syndrome.

In the vulnerable host, chronic cavitary lesions develop, with a predilection for the upper lobe, resembling the secondary form of tuberculosis. The most common manifestations are productive cough, fever, night sweats, and weight loss.

Disseminated disease most often develops as an acute and fulminating infection in the very old or the very young or in persons with compromised immune function. Although the macrophages of the reticuloendothelial system can remove the fungi from the bloodstream, they are unable to destroy them. Characteristically, this form of the disease presents with a high fever, generalized lymph node enlargement, hepatosplenomegaly, muscle wasting, anemia, leukopenia, and thrombocytopenia. There may be hoarseness, ulcerations of the mouth and tongue, nausea, vomiting, diarrhea, and abdominal pain. Often, meningitis becomes a dominant feature of the disease. Persons with blastomycosis may experience cutaneous infections that induce pseudoepitheliomatous hyperplasia, which may be mistaken for squamous cell carcinoma.

Skin tests similar to the tuberculin test can be used to detect exposure to *Histoplasma* and *Coccidioides*. There is no reliable skin test for *Blastomyces*. The diagnosis of acute infection is usually made by direct visualization of the organism in tissue sections or sputum culture. Serologic tests that detect antibodies against the specific fungi are available, but lack sensitivity and specificity.

Treatment depends on the severity of infection. Persons without associated risk factors such as HIV infection or without specific evidence of progressive disease usually can be treated without antifungal therapy. The oral or intravenous antifungal drugs are used in the treatment of persons with progressive disease.

In summary, respiratory infections are the most common cause of respiratory illness. They include the common cold, rhinosinusitis, influenza, the pneumonias, tuberculosis, and fungal infections. The common cold occurs more frequently than any other respiratory infection. The fingers are the usual source of transmission, and the most common portals of entry are the nasal mucosa and the conjunctiva of the eye. Rhinosinusitis refers to acute, subacute, or chronic infection of the nasal mucosa and paranasal sinuses. The influenza virus is one of the most important causes of upper respiratory tract infections. There are three types of influenza viruses: types A, B, and C. Type A is further divided into subtypes based on two surface antigens, HA and NA. Epidemics

occur through mutations or antigenic shifts in HA and NA that allow the virus to escape most host antibodies.

Pneumonia describes an infection of the parenchymal tissues of the lung, such as the alveoli and bronchioles. Loss of the cough reflex, damage to the ciliated endothelium that lines the respiratory tract, or impaired immune defenses predispose to development of pneumonia. Pneumonia is being increasingly classified as community-acquired (infections that occur outside the hospital) and hospital-acquired (infections that result from organisms in the hospital environment). Persons with compromised immune function constitute a special concern in both categories. The most common cause of community-acquired pneumonia is *S. pneumoniae.* Legionnaires disease is a form of bronchopneumonia caused by the gram-negative bacillus *L. pneumophila.* Viral or atypical pneumonia can occur as a primary infection, such as that caused by influenza virus, or as a complication of other viral infections, such as measles or chickenpox. Viral and atypical pneumonias involve the interstitium of the lung and often masquerade as a chest cold.

Tuberculosis is a chronic respiratory infection caused by *M. tuberculosis,* which is spread by minute, invisible particles called *droplet nuclei.* Tuberculosis is a particular threat among HIV-infected persons, persons from countries with a high incidence of tuberculosis, and residents of high-risk congregate settings such as correctional facilities, drug treatment facilities, and homeless shelters. The tubercle bacillus incites a distinctive chronic inflammatory response referred to as *granulomatous inflammation.* The destructiveness of the disease results from the cell-mediated immune response that the bacillus evokes rather than its inherent destructive capabilities. The treatment of tuberculosis, which has been complicated by outbreaks of drug-resistant forms of the disease, requires multidrug regimens taken over a relatively long period of time.

Infections caused by the fungi *H. capsulatum* (histoplasmosis), *C. immitis* (coccidioidomycosis), and *B. dermatitidis* (blastomycosis) produce pulmonary manifestations that resemble tuberculosis. These infections are common but seldom serious unless they produce progressive destruction of lung tissue or the infection disseminates to organs and tissues outside the lungs.

Cancer of the Lung

Lung cancer is the leading cause of cancer deaths among men and women in the United States. In 2004, it was responsible for the deaths of approximately 93,000 men and 80,500 women.[45] The increase in lung cancer incidence and deaths over the past 50 years has coincided closely with the increase in cigarette smoking over the same period. Between 1980 and 1998, lung cancer mortality rates decreased for persons younger than 55 years and increased for those older than 65 years, reflecting generational patterns in smoking prevalence.[46,47] Because lung cancer often is far advanced before it is discovered, the prognosis is generally poor. The overall 5-year survival rate is 13% to 15%, a dismal statistic that has not changed since the late 1960s.

With regard to carcinogenic influences, there is strong evidence that smoking is to a large extent responsible for the genetic changes that convert normal bronchial cells to cancer cells. Other influences may act in concert with smoking or may by themselves be responsible for some lung cancers. For example, there is increased incidence of lung cancer in asbestos workers and workers exposed to dusts containing arsenic, chromium, nickel, and vinyl chloride.

Most primary lung tumors (about 95%) arise from the bronchial epithelium (bronchogenic carcinoma). The remaining 5% are a miscellaneous group that includes bronchial carcinoid tumors (neuroendocrine tumors), bronchial gland tumors, fibrosarcomas, and lymphomas. The lung is also a frequent site of metastasis from cancers in other parts of the body.

BRONCHOGENIC CARCINOMA

Bronchogenic carcinomas are aggressive, locally invasive, and widely metastatic tumors that arise from the epithelial lining of the major bronchi. These tumors begin as small mucosal lesions that may follow one of several patterns of growth. They may form intraluminal masses that invade the bronchial mucosa and infiltrate the peribronchial connective tissue, or they may form large, bulky masses that extend into the adjacent lung tissue. Some large tumors undergo central necrosis and acquire local areas of hemorrhage, whereas some invade the pleural cavity and chest wall and spread to adjacent intrathoracic structures.[21] All forms of bronchiogenic carcinomas, especially small-cell lung carcinoma, have the capacity to synthesize bioactive products and produce paraneoplastic syndromes (to be discussed).

Bronchogenic carcinomas can be subdivided into four major categories: squamous cell lung carcinoma (25% to 40%), adenocarcinoma (25% to 40%), small-cell carcinoma (20% to 25%), and large-cell carcinoma (10% to 15%).[21] For purposes of staging and treatment, bronchogenic cancers are commonly identified as small-cell lung cancer (SCLC) or non–small-cell lung cancer (NSCLC). The main reason for this classification is that most SCLCs have metastasized by the time of diagnosis and hence are not amenable to cancer surgery. They are usually best treated with chemotherapy, with or without radiation.

Small-Cell Lung Cancers

Small-cell lung cancers are characterized by a distinctive cell type—small, round to oval cells that are approximately the size of a lymphocyte.[21] The cells grow in clusters that exhibit neither glandular nor squamous organization.

This type of lung cancer has the strongest association with cigarette smoking and is rarely observed in someone who has not smoked.[47] The SCLCs are highly malignant, tend to infiltrate widely, disseminate early in their course, and rarely are resectable. About 70% have detectable metastases at the time of diagnosis.[48] Brain metastases are particularly common with SCLC and may provide the first evidence of the tumor. Without treatment, one half of persons with SCLC die within 12 to 15 weeks.

Non–Small-Cell Lung Cancers

The NSCLCs include squamous cell carcinomas, adenocarcinomas, and large-cell carcinomas. *Squamous cell carcinoma* is found most commonly in men and is closely correlated with a smoking history. Squamous cell carcinoma tends to originate in the central bronchi as an intraluminal growth and is thus more amenable to early detection through cytologic examination of the sputum than other forms of lung cancer. It tends to spread centrally into major bronchi and hilar lymph nodes and disseminates outside the thorax later than other types of bronchogenic cancers.

Currently, *adenocarcinoma* is the most common type of lung cancer found in North America.[22] Its association with cigarette smoking is weaker than for squamous cell carcinoma. It is the most common type of lung cancer in women and nonsmokers. Adenocarcinomas can have their origin in either the bronchiolar or alveolar tissues of the lung. These tumors tend to be located more peripherally than squamous cell sarcomas and sometimes are associated with areas of scarring (Fig. 21-7). The scars may be due to old infarcts, metallic foreign bodies, wounds, and granulomatous infections such as tuberculosis. In general, adenocarcinomas have a poorer stage-for-stage prognosis compared with squamous cell carcinomas.

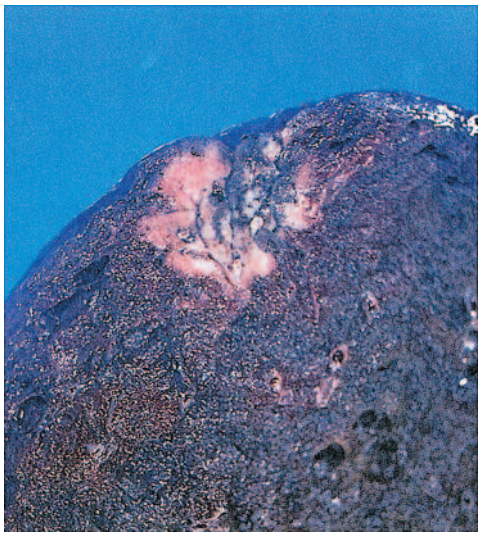

FIGURE 21-7 Adenocarcinoma of the lung. A peripheral tumor in the upper right lobe of the lung has an irregular border and a tan or gray cut surface. (From Travis W. D., Beasley M. B., Rubin E. [2005]. The respiratory system. In Rubin E., Gorstein F., Rubin R., et al. [Eds.], *Rubin's pathology: Clinicopathologic foundations of medicine* [4th ed., p. 649]. Philadelphia: Lippincott Williams & Wilkins.)

Large-cell carcinomas have large polygonal cells. They constitute a group of neoplasms that are highly anaplastic and difficult to categorize as squamous or adenocarcinoma. They tend to occur in the periphery of the lung, invading subsegmental bronchi and larger airways. They have a poor prognosis because of their tendency to spread to distant sites early in their course.

Clinical Features

Manifestations. The manifestations of lung cancer are extremely variable, depending on the location of the tumor, the presence of distant metastasis, and the occurrence of paraneoplastic syndromes. Often the malignancy develops insidiously, giving little or no warning of its presence. Because its symptoms are similar to those associated with smoking and chronic bronchitis, they often are disregarded.

The manifestations of lung cancer can be divided into three categories: those due to involvement of the lung and adjacent structures, the effects of local spread and metastasis, and the nonmetastatic paraneoplastic manifestations involving endocrine, neurologic, and connective tissue function. As with other cancers, lung cancer also causes nonspecific symptoms such as anorexia and weight loss.

Many of the manifestations of lung cancers result from local irritation and obstruction of the airways and from invasion of the mediastinum and pleural space. The earliest symptoms usually are chronic cough, shortness of breath, and wheezing because of airway irritation and obstruction. Hemoptysis (*i.e.*, blood in the sputum) occurs when the lesion erodes blood vessels. Pain receptors in the chest are limited to the parietal pleura, mediastinum, larger blood vessels, and peribronchial afferent vagal fibers. Dull, intermittent, poorly localized retrosternal pain is common in tumors that involve the mediastinum. Pain becomes persistent, localized, and more severe when the disease invades the pleura.

Tumors that invade the mediastinum may cause hoarseness because of the involvement of the recurrent laryngeal nerve and cause difficulty in swallowing because of compression of the esophagus. An uncommon complication called the *superior vena cava syndrome* can occur in some persons with mediastinal involvement. Interruption of blood flow in this vessel usually results from compression by the tumor or involved lymph nodes. The disorder can interfere with venous drainage from the head, neck, and chest wall. The outcome is determined by the speed with which the disorder develops and the adequacy of the collateral circulation.

Tumors adjacent to the visceral pleura often insidiously produce pleural effusion. This effusion can compress the lung and cause atelectasis and dyspnea. It is less likely to cause fever, pleural friction rub, or pain than pleural effusion resulting from other causes.

Metastatic spread occurs by way of lymph channels and the vascular system. Metastases already exist in 50%

of patients presenting with evidence of lung cancer and develop eventually in 90% of patients. The most common sites of metastases are the brain, bone, and liver.

All varieties of bronchogenic carcinomas, especially SCLCs, have the capacity to synthesize bioactive products and produce paraneoplastic syndromes (see Chapter 5). These syndromes include hypercalcemia from secretion of parathyroid-like peptide, Cushing syndrome from adrenocorticotropic hormone (ACTH) secretion, inappropriate secretion of antidiuretic hormone (ADH), neuromuscular syndromes (*e.g.*, Eaton-Lambert syndrome), and hematologic disorders (*e.g.*, migratory thrombophlebitis, nonbacterial endocarditis, disseminated intravascular coagulation). Manifestations of the paraneoplastic syndrome may precede the onset of other signs of lung cancer and may lead to discovery of an occult tumor. Hypercalcemia is seen most often in persons with squamous cell carcinoma, hematologic syndromes in persons with adenocarcinomas, and the remaining syndromes in persons with SCLCs. Neurologic or muscular symptoms can develop 6 months to 4 years before the lung tumor is detected. One of the more common of these problems is weakness and wasting of the proximal muscles of the pelvic and shoulder girdles, with decreased deep tendon reflexes but without sensory changes.

Diagnosis and Treatment. The diagnosis of lung cancer is based on a careful history and physical examination and other tests such as chest radiography, bronchoscopy, cytologic studies (Papanicolaou [Pap] test) of the sputum or bronchial washings, percutaneous needle biopsy of lung tissue, and scalene lymph node biopsy.[46] CT scans, magnetic resonance imaging (MRI) studies, and ultrasonography are used to locate lesions and evaluate the extent of the disease. Positron emission tomography (PET) is a noninvasive alternative for identifying metastatic lesions in the mediastinum or distant sites. Persons with SCLC should also have a CT scan or MRI of the brain for detection of metastasis.

Treatment methods for NSCLC include surgery, radiation therapy, and chemotherapy.[46] These treatments may be used singly or in combination. Surgery is used for the removal of small, localized NSCLC tumors. It can involve a lobectomy, pneumonectomy, or segmental resection of the lung. Radiation therapy can be used as a definitive or main treatment modality, as part of a combined treatment plan, or for palliation of symptoms. Because of the frequency of metastases, chemotherapy often is used in treating lung cancer. Combination chemotherapy, which uses a regimen of several drugs, usually is used. New targeted treatments are under development with the goal of increasing survival and ultimately providing a cure for this type of cancer.

Therapy for SCLC is based on chemotherapy and radiation therapy.[46,48,49] Because SCLC may metastasize to the brain, prophylactic cranial irradiation is often indicated. Advances in the use of combination chemotherapy, along with thoracic irradiation, have improved the outlook for persons with SCLC. In persons who achieve a complete remission from SCLC, the brain is the most frequent site of relapse. About half of such persons develop clinical metastases within 3 years. Newer combination chemotherapy regimens and targeted therapies are being developed in hopes of providing treatment alternatives that increase survival and produce fewer treatment liabilities.

In summary, cancer of the lung is a leading cause of death among men and women in the United States. The increased death rate from lung cancer has coincided with an increase in cigarette smoking. Industrial hazards, such as exposure to asbestos, increase the risk for development of lung cancer. Because lung cancer develops insidiously, it often is far advanced before it is diagnosed; a fact that helps explain the poor 5-year survival rate.

Bronchogenic carcinoma, which accounts for 95% of all primary lung cancers, can be subdivided into SCLC and NSCLCs (squamous cell carcinoma, adenocarcinoma, large-cell carcinoma). The manifestations of lung cancer can be attributed to the involvement of the lung and adjacent structures, the effects of local spread and metastasis, and paraneoplastic syndromes involving endocrine, neurologic, and hematologic dysfunction. As with other cancers, lung cancer causes nonspecific symptoms such as anorexia and weight loss. Treatment methods for lung cancer include surgery, irradiation, and chemotherapy.

Respiratory Disorders in Children

Acute respiratory disease is a common cause of illness in infancy and childhood. The etiology and course of these disorders are influenced by a number of factors, including the age of the child, immaturity of the respiratory system, preexisting medical problems, and season of the year. This section focuses on (1) lung development, with an emphasis on the developmental basis for lung disorders in children; (2) respiratory disorders in the neonate; and (3) respiratory infections in children. A discussion of bronchial asthma in children and cystic fibrosis is included in Chapter 22.

LUNG DEVELOPMENT

Although other body systems are physiologically ready for extrauterine life as early as 25 weeks of gestation, the lungs require much longer. Immaturity of the respiratory system is a major cause of morbidity and mortality in infants born prematurely. Even at birth, the lungs are not fully mature, and additional growth and maturation continue well into childhood.

Lung development may be divided into five stages: the embryonic, glandular, canicular, saccular, and alveolar periods.[50] The first three phases are devoted to development of the conducting airways, and the last two phases are devoted to development of the gas exchange portion

of the lung. By the 25th to 28th weeks of gestation, sufficient terminal air sacs are present to permit survival. It is also during this period that the type II alveolar cells, which produce surfactant, begin to function. Lung development is incomplete at birth; an infant is born with only one eighth to one sixth the adult number of alveoli. Alveoli continue to be formed during early childhood, reaching the adult number of approximately 300 million alveoli by 5 to 6 years of age.[50]

Ventilation in the Neonate

Effective ventilation requires coordinated interaction between the muscles of the upper airways, including those of the pharynx and larynx, the diaphragm, and the intercostal muscles of the chest wall. In the infant, the diaphragm inserts more horizontally than in the adult. As a result, contraction of the diaphragm tends to draw the lower ribs inward, especially if the infant is placed in the horizontal position. The intercostal muscles, which normally lift the ribs during inspiration, are not fully developed in the infant.[51] Instead, they function largely to stabilize the chest. Under circumstances such as crying, the intercostal muscles of the neonate function together with the diaphragm to splint the chest wall and prevent its collapse.

The chest wall of the neonate is highly compliant. A striking characteristic of neonatal breathing is the paradoxical inward movement of the upper chest during inspiration, especially during active sleep. Normally, the infant's lungs also are compliant, which is advantageous to the infant with its compliant chest cage because it takes only small changes in inspiratory pressure to inflate a compliant lung. However, with respiratory disorders that decrease lung compliance, the diaphragm must generate more negative pressure; as a result, the compliant chest wall structures are sucked inward. *Retractions* are abnormal inward movements of the chest wall during inspiration; they may occur intercostally (between the ribs), in the substernal or epigastric area, and in the supraclavicular spaces (Fig. 21-8).

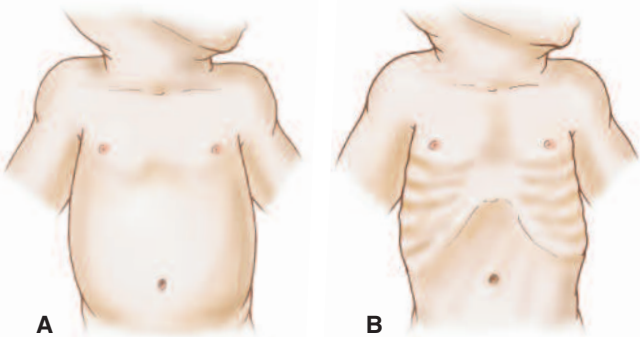

FIGURE 21-8 (**A**) Normal inspiratory appearance of the chest during unobstructed breathing. (**B**) Sternal and intercostal retraction during obstructed breathing in the neonate.

Airway Resistance

Normal lung inflation requires uninterrupted movement of air through the extrathoracic airways (*i.e.,* nose, pharynx, larynx, and upper trachea) and intrathoracic airways (*i.e.,* bronchi and bronchioles). The neonate (0 to 4 weeks of age) breathes predominantly through the nose and does not adapt well to mouth breathing. Any obstruction of the nose or nasopharynx may increase upper airway resistance and increase the work of breathing.

The airways of the infant and small child are much smaller than those of the adult. Because airflow is directly related to the fourth power of the radius, relatively small amounts of mucus secretion, edema, or airway constriction can produce marked changes in airflow. *Nasal flaring* is a method that infants use to take in more air. This method of breathing increases the size of the nares and decreases the resistance of the small airways.

Normally, the extrathoracic airways in the infant narrow during inspiration and widen during expiration, and the intrathoracic airways widen during inspiration and narrow during expiration. This occurs because the pressure inside the extrathoracic airways reflects the intrapleural pressures that are generated during breathing, whereas the pressure outside the airways is similar to atmospheric pressure. Thus, during inspiration, the pressure inside becomes more negative, causing the airways to narrow, and during expiration it becomes more positive, causing them to widen. In contrast to the extrathoracic airways, the pressure outside the intrathoracic airways is equal to the intrapleural pressure. These airways widen during inspiration as the surrounding intrapleural pressure becomes more negative and pulls them open, and they narrow during expiration as the surrounding pressure becomes more positive.

Lung Volumes and Gas Exchange

The functional residual capacity, which is the air left in the lungs at the end of normal expiration, plays an important role in gas exchange in the infant. In the infant, the functional residual capacity represents a higher lung volume than in the older child or adult. This higher end-expiratory volume results from a more rapid respiratory rate, which leaves less time for expiration. However, the increased residual volume is important to the neonate because it holds the airways open throughout all phases of respiration; it favors the reabsorption of intrapulmonary fluids; and it maintains more uniform lung expansion and enhances gas exchange. During sleep, the tone of the upper airway muscles is reduced, so that the time spent in expiration is shorter and the intercostal activity that stabilizes the chest wall is less; this produces a lower end-expiratory volume and less optimal gas exchange during active sleep.[52]

Control of Ventilation

Fetal blood oxygen (PO_2) levels normally range from 25 to 30 mm Hg, and carbon dioxide (PCO_2) levels range

from 45 to 50 mm Hg, independent of any respiratory movements. Switching to oxygen derived from the aerated lung at birth causes an immediate increase in PO_2 to approximately 50 mm Hg; within a few hours, it increases to approximately 70 mm Hg.[53] These levels, which greatly exceed fetal levels, cause the chemoreceptors (see Chapter 20) to become silent for several days. Although the infant's PO_2 may fluctuate during this critical time, the chemoreceptors do not respond appropriately. It is not until several days after birth that the chemoreceptors "reset" their PO_2 threshold; only then do they contribute to the control of breathing. However, the response seems to be biphasic, with an initial hyperventilation followed by a decreased respiratory rate and even apnea. In normal neonates, particularly in preterm infants, breathing patterns and respiratory reflexes depend on the arousal state.[52] Periodic breathing and apnea are characteristic of premature infants and reflect patterns of fetal breathing. The fact that they occur with sleep and disappear during wakefulness underscores the importance of arousal.

ALTERATIONS IN BREATHING PATTERNS

Most respiratory disorders in infants produce a decrease in lung compliance (restrictive lung disorders) or an increase in airway resistance manifested by changes in breathing patterns, rib cage distortion (retractions), audible sounds, and use of accessory muscles.[53]

Children with restrictive lung disorders, such as pulmonary edema or respiratory distress syndrome, breathe at faster rates, and their respiratory excursions are shallow. *Grunting* is an audible noise emitted during expiration. An expiratory grunt is common as the child tries to raise the end-expiratory pressure and thus prolong the period of oxygen and carbon dioxide exchange across the alveolar capillary membrane.

Increased airway resistance can occur in either the extrathoracic or intrathoracic airways. When the obstruction is in the extrathoracic airways, inspiration is more prolonged than expiration. *Nasal flaring* (enlargement of the nares) helps reduce the nasal resistance and maintain airway patency. It can be a sign of increased work of breathing and is a significant finding in an infant. *Inspiratory retractions,* or pulling in of the soft tissue surrounding the cartilaginous and bony thorax, is often observed with airway obstruction in infants and small children (see Fig. 21-8). In conditions such as croup, the pressures distal to the point of obstruction must become more negative to overcome the resistance; this causes collapse of the distal airways, and the increased turbulence of air moving through the obstructed airways produces an audible crowing sound during inspiration called *stridor*.

When the obstruction is in the intrathoracic airways, as occurs with bronchiolitis and bronchial asthma, expiration is prolonged and the child makes use of the accessory expiratory muscles (abdominals). Rib cage retractions may also be present. Intrapleural pressure becomes more positive during expiration because of air trapping; this causes collapse of intrathoracic airways and produces an audible wheezing or whistling sound during expiration.

RESPIRATORY DISORDERS IN THE NEONATE

The neonatal period is one of transition from placental dependency to air breathing. This transition requires functioning of the surfactant system, conditioning of the respiratory muscles, and establishment of parallel pulmonary and systemic circulations. Respiratory disorders develop in infants who are born prematurely or who have other problems that impair this transition. Among the respiratory disorders of the neonate are the respiratory distress syndrome, bronchopulmonary dysplasia, and persistent fetal circulation (*i.e.,* delayed closure of the ductus arteriosus and foramen ovale).

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), also known as *hyaline membrane disease,* is one of the most common causes of respiratory disease in premature infants.[54,55] In these infants, pulmonary immaturity, together with surfactant deficiency, lead to alveolar collapse (Fig. 21-9). The type II

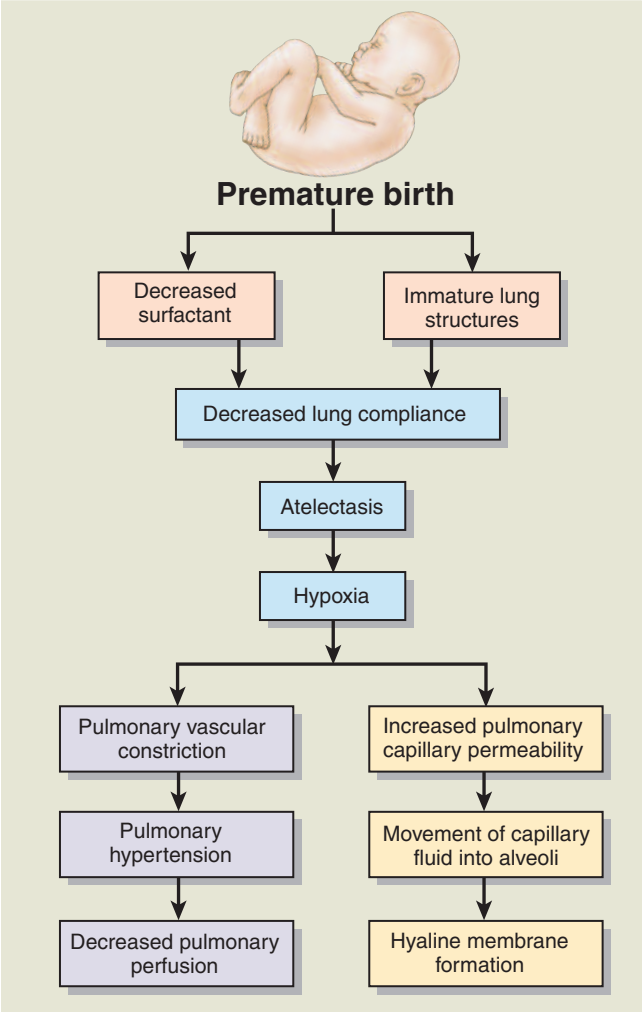

FIGURE 21-9 Pathogenesis of respiratory distress syndrome (RSD) in the infant.

alveolar cells that produce surfactant do not begin to mature until approximately the 25th to 28th weeks of gestation; consequently, many premature infants are born with poorly functioning type II alveolar cells and have difficulty producing sufficient amounts of surfactant. The incidence of RDS is higher among preterm male infants, white infants, infants of diabetic mothers, and those subjected to asphyxia, cold stress, precipitous deliveries, and delivery by cesarean section (when performed before the 38th week of gestation).

Surfactant synthesis is influenced by several hormones, including insulin and cortisol. Insulin tends to inhibit surfactant production; this explains why infants of insulin-dependent diabetic mothers are at increased risk for development of RDS. Cortisol can accelerate maturation of type II cells and formation of surfactant. The reason that premature infants born by cesarean section presumably are at greater risk for development of RDS is because they are not subjected to the stress of vaginal delivery, which is thought to increase the infants' cortisol levels. These observations have led to administration of corticosteroid drugs before delivery to mothers with infants at high risk for development of RDS.[54]

Surfactant reduces the surface tension in the alveoli, thereby equalizing the retractive forces in the large and small alveoli and reducing the amount of pressure needed to inflate and hold the alveoli open. Without surfactant, the large alveoli remain inflated while the small alveoli become difficult to inflate. At birth, the first breath requires high inspiratory pressures to expand the lungs. With normal levels of surfactant, the lungs retain up to 40% of the residual volume after the first breath, and subsequent breaths require far lower inspiratory pressures. With a surfactant deficiency, the lungs collapse between breaths, making the infant work as hard with each successive breath as with the first breath. The airless portions of the lungs become stiff and noncompliant. A hyaline membrane forms inside the alveoli as protein- and fibrin-rich fluids are pulled into the alveolar spaces. The fibrin-hyaline membrane constitutes a barrier to gas exchange, leading to hypoxemia and carbon dioxide retention, a condition that further impairs surfactant production.

Infants with RDS present with multiple signs of respiratory distress, usually within the first 24 hours of birth. Central cyanosis is a prominent sign. Breathing becomes more difficult, and retractions occur as the infant's soft chest wall is pulled in as the diaphragm descends. Grunting sounds occur during expiration. As the tidal volume drops because of atelectasis, the respiration rate increases (usually to 60 to 120 breaths/minute) in an effort to maintain normal minute ventilation. Fatigue may develop rapidly because of the increased work of breathing. The stiff lung of infants with RDS also increases resistance to blood flow in the pulmonary circulation. As a result, a hemodynamically significant patent ductus arteriosus may develop in infants with RDS (see Chapter 18).

The basic principles of treatment for infants with suspected RDS focus on the provision of supportive care, including gentle handling and minimal disturbance.[54] An isolette (incubator) or radiant warmer is used to prevent hypothermia and increased oxygen consumption. Continuous cardiorespiratory monitoring is needed. Monitoring of blood glucose and prevention of hypoglycemia are also recommended. Oxygen levels can be assessed through an arterial line (umbilical) or by a transcutaneous oxygen sensor. Treatment includes administration of supplemental oxygen, continuous positive airway pressure through nasal prongs, and often assisted mechanical ventilation.

Exogenous surfactant therapy is used to prevent and treat RDS.[54,55] The surfactants are suspended in saline and administered into the airways, usually through an endotracheal tube. The treatment often is initiated soon after birth in infants who are at high risk for RDS.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that develops in premature infants who were treated with mechanical ventilation, mainly for RDS.[54–57] The condition is considered to be present if the neonate is oxygen dependent at 36 weeks after gestation. The disorder is thought to be a response of the premature lung to early injury. High inspired oxygen concentration and injury from positive-pressure ventilation (*i.e.,* barotrauma) have been implicated. Newer therapies such as administration of surfactants, high-frequency ventilation, and prenatal or postnatal administration of corticosteroids may have altered the severity of BPD, but the condition remains a major health problem.[56,57]

Bronchopulmonary dysplasia is characterized by chronic respiratory distress, persistent hypoxemia when breathing room air, reduced lung compliance, increased airway resistance, and severe expiratory flow limitation. There is a mismatching of ventilation and perfusion with development of hypoxemia and hypercapnia. Pulmonary vascular resistance may be increased and pulmonary hypertension and cor pulmonale (*i.e.,* right heart failure associated with lung disease) may develop. The infant with BPD may have tachycardia, shallow breathing, chest retractions, cough, barrel chest, and poor weight gain. In infants with right heart failure, tachycardia, tachypnea, hepatomegaly, and periorbital edema develop. Clubbing of the fingers occurs in children with severe disease.

The treatment of BPD includes mechanical ventilation and administration of adequate oxygenation. Weaning from ventilation is accomplished gradually, and some infants may require ventilation at home. Rapid lung growth occurs during the first year of life, and lung function usually improves. Adequate nutrition is essential for recovery of infants with BPD.

Most adolescents and young adults who had severe BPD during infancy have some degree of pulmonary dysfunction, consisting of airway obstruction, airway hyperreactivity, or hyperinflation.

RESPIRATORY INFECTIONS IN CHILDREN

In children, respiratory tract infections are common, and although they are troublesome, they usually are not serious. Frequent infections occur because the immune system of infants and small children has not been exposed to many common pathogens; consequently, they tend to

contract infections with each new exposure.[55,58] Although most of these infections are not serious, the small size of an infant or child's airways tends to foster impaired airflow and obstruction. For example, an infection that causes only sore throat and hoarseness in an adult may result in serious airway obstruction in a small child.

Upper Airway Infections

Acute upper airway infections are important in infants and small children. They include croup (laryngotracheobronchitis) and epiglottitis. Croup is the more common one, and it usually is benign and self-limited. Epiglottitis is a rapidly progressive and life-threatening condition. The site of involvement is illustrated in Figure 21-10, and the characteristics of both infections are described in Table 21-2.

Obstruction of the upper airways because of infection tends to exert its greatest effect during the inspiratory phase of respiration. Movement of air through an obstructed upper airway, particularly the vocal cords in the larynx, causes stridor.[59] Impairment of the expiratory phase of respiration also can occur, causing wheezing. With mild to moderate obstruction, inspiratory stridor is more prominent than expiratory wheezing because the airways tend to dilate with expiration. When the swelling and obstruction become severe, the airways no longer can dilate during expiration, and both stridor and wheezing occur.

Cartilaginous support of the trachea and the larynx is poorly developed in infants and small children. These structures are soft and tend to collapse when the airway is obstructed and the child cries, causing the inspiratory pressures to become more negative. When this happens, the stridor and inspiratory effort are increased. The phenomenon of airway collapse in the small child is analogous to what happens when a thick beverage, such as a milkshake, is drunk through a soft paper or plastic straw. The straw collapses when the negative pressure produced by the sucking effort exceeds the flow of liquid through the straw.

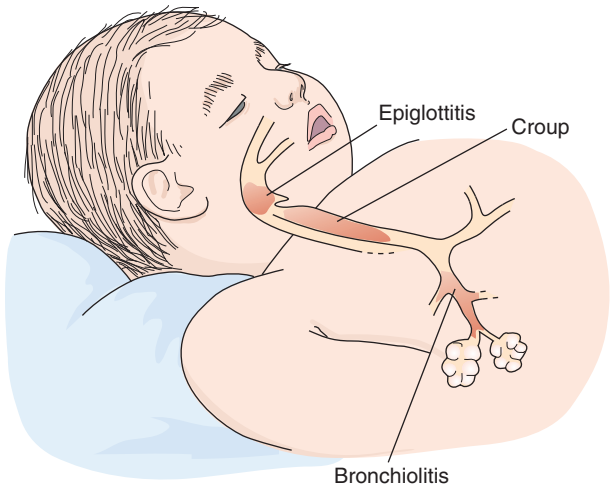

FIGURE 21-10 Location of airway obstruction in epiglottitis, acute laryngotracheobronchitis (croup), and bronchiolitis. (Courtesy of Carole Russell Hilmer, C.M.I.)

Viral Croup. Croup is characterized by inspiratory stridor, hoarseness, and a barking cough. The British use the term *croup* to describe the cry of the crow or raven, and this is undoubtedly how the term originated.

Viral croup, more appropriately called *acute laryngotracheobronchitis,* is a viral infection that affects the larynx, trachea, and bronchi. The parainfluenza viruses account for approximately 75% all cases; the remaining 25% are caused by adenoviruses, respiratory syncytial virus, influenza A and B viruses, and measles virus.[59–62] Viral croup usually is seen in children 3 months to 5 years of age. The condition may affect the entire laryngotracheal tree, but because the subglottic area is the narrowest part of the respiratory tree in this age group, the obstruction usually is greatest in this area. For example, the subglottic airway in the 1- to 2-year-old child is approximately 6.5 mm in diameter, and 1 mm of edema can reduce the cross-sectional area by 50%.[59]

Although the respiratory manifestations of croup often appear suddenly, they usually are preceded by upper respiratory infections that cause rhinorrhea (*i.e.,* runny nose), coryza (*i.e.,* common cold), hoarseness, and a low-grade fever. In most children, the manifestation of croup advances only to stridor and slight dyspnea before they begin to recover. The symptoms usually subside when the child is exposed to moist air. For example, letting the bathroom shower run and then taking the child into the bathroom often brings prompt and dramatic relief of symptoms. Exposure to cold air also seems to relieve the airway spasm; often, the severe symptoms are relieved simply because the child is exposed to cold air on the way to the hospital emergency department.

Airway obstruction may progress in some children. As obstruction increases, the stridor becomes continuous and is associated with nasal flaring with substernal and intercostal retractions. Agitation and crying aggravate the signs and symptoms, and the child prefers to sit up or be held upright. In the cyanotic, pale, or obstructed child, any manipulation of the pharynx, including use of a tongue depressor, can cause cardiorespiratory arrest and should be done only in a medical setting that has the facilities for emergency airway management.

Treatment of viral croup is based on symptoms. Children with mild croup, as indicated by a barking cough and no stridor, usually require only supportive care with oral hydration and minimal handling. A humidifier or mist therapy may be used. Children with stridor at rest require additional interventions. Nebulized racemic epinephrine (L-epinephrine and D-epinephrine) is commonly used because of its rapid onset of action. Corticosteroids may be used to decrease the edema of the laryngeal mucosa through their anti-inflammatory action. Children with progressive stridor, severe stridor at rest, respiratory distress, hypoxia, cyanosis, or depressed mental status should be hospitalized.[58]

Spasmodic Croup. Spasmodic croup manifests with symptoms similar to those of acute viral croup. Because the child is afebrile and lacks other manifestations of the

TABLE 21-2 Characteristics of Epiglottitis, Croup, and Bronchiolitis in Small Children

Characteristics	Epiglottitis	Croup	Bronchiolitis
Common causative agent	*Haemophilus influenzae* type B bacterium	Mainly parainfluenza virus	Respiratory syncytial virus
Most commonly affected age group	2–7 years (peak 3–5 years)	3 months to 5 years	Less than 2 years (most severe in infants younger than 6 months)
Onset and preceding history	Sudden onset	Usually follows symptoms of a cold	Preceded by stuffy nose and other signs
Prominent features	Child appears very sick and toxic Sits with mouth open and chin thrust forward Low-pitched stridor, difficulty swallowing, fever, drooling, anxiety *Danger of airway obstruction and asphyxia*	Stridor and a wet, barking cough Usually occurs at night Relieved by exposure to cold or moist air	Breathlessness, rapid, shallow breathing, wheezing, cough, and retractions of lower ribs and sternum during inspiration
Usual treatment	Hospitalization Intubation or tracheotomy Treatment with appropriate antibiotic	Hydration Mist tent or vaporizer Administration of oxygen Nebulized epinephrine	Supportive treatment, administration of oxygen and hydration

viral prodrome, it is thought that it may have an allergic origin. Spasmodic croup characteristically occurs at night and tends to recur with respiratory tract infections. The episode usually lasts several hours and may recur several nights in a row.

Most children with spasmodic croup can be effectively managed at home. An environment of high humidification (*i.e.*, cold-water room humidifier or taking the child into a bathroom with a warm, running shower) lessens irritation and prevents drying of secretions.

Epiglottitis. Acute epiglottitis is a dramatic, potentially fatal condition that is characterized by inflammatory edema of the supraglottic area, including the epiglottis and pharyngeal structures (see Fig. 21-10), and that comes on suddenly, bringing danger of airway obstruction and asphyxia.[59,60] In the past, the *H. influenzae* type B bacterium was the most commonly identified etiology. It is seen less commonly since the widespread use of immunization against *H. influenzae* type B. Therefore, other agents such as *Streptococcus pyogenes*, *S. pneumoniae*, and *S. aureus* now represent the most common cause of pediatric epiglottitis.[59]

The child appears pale, toxic, and lethargic and assumes a distinctive position—sitting up with the mouth open and the chin thrust forward. There is difficulty in swallowing, a muffled voice, drooling, fever, and extreme anxiety. Moderate to severe respiratory distress is evident. There is inspiratory and sometimes expiratory stridor, flaring of the nares, and inspiratory retractions of the suprasternal notch and supraclavicular and intercostal spaces. Within a matter of hours, epiglottitis may progress to complete obstruction of the airway and death unless adequate treatment is instituted. Epiglottitis is a medical emergency and immediate establishment of an airway by endotracheal tube or tracheotomy usually is needed. If epiglottitis is suspected, the child should never be forced to lie down because this causes the epiglottis to fall backward and may lead to complete airway obstruction. Examination of the throat with a tongue blade or other instrument may cause cardiopulmonary arrest and should be done only by medical personnel experienced in intubation of small children. It also is unwise to attempt any procedure, such as drawing blood, that would heighten the child's anxiety because this also could precipitate airway spasm and cause death. Recovery from epiglottitis usually is rapid and uneventful after an adequate airway has been established and appropriate antibiotic therapy has been initiated.

Lower Airway Infections

Lower airway infections produce air trapping with prolonged expiration. Wheezing results from bronchospasm, mucosal inflammation, and edema. The child presents with increased expiratory effort, increased respiratory rate, and wheezing. If the infection is severe, there also are marked intercostal retractions and signs of impending respiratory failure.

Acute bronchiolitis is a viral infection of the lower airways (see Fig. 21-10), most commonly caused by the respiratory syncytial virus.[62,63] Other viruses, such as parainfluenza 3 virus and some adenoviruses, as well as mycoplasmas, also are causative. The infection produces inflammatory obstruction of the small airways and necrosis of the cells lining the lower airways. It usually occurs during the first 2 years of life, with a peak incidence between 3 to 6 months of age. The source of infection usually is a family member with a minor respiratory illness. Older children and adults tolerate bronchiolar edema much better than infants and do not manifest the clinical picture of bronchiolitis. Because the resistance to

airflow in a tube is related to the fourth power of the radius, even minor swelling of bronchioles in an infant can produce profound changes in airflow.

Most affected infants in whom bronchiolitis develops have a history of a mild upper respiratory tract infection. These symptoms usually last several days and may be accompanied by fever and diminished appetite. There is then a gradual development of respiratory distress, characterized by a wheezy cough, dyspnea, and irritability. The infant usually is able to take in sufficient air but has trouble exhaling it. Air becomes trapped in the lung distal to the site of obstruction and interferes with gas exchange. Hypoxemia and, in severe cases, hypercapnia may develop. Airway obstruction may produce air trapping and hyperinflation of the lungs or collapse of the alveoli. Infants with acute bronchiolitis have a typical appearance, marked by breathlessness with rapid respirations, a distressing cough, and retractions of the lower ribs and sternum. Crying and feeding exaggerate these signs. Wheezing and rales may or may not be present, depending on the degree of airway obstruction. In infants with severe airway obstruction, wheezing decreases as the airflow diminishes. Usually, the most critical phase of the disease is the first 48 to 72 hours. Cyanosis, pallor, listlessness, and sudden diminution or absence of breath sounds indicate impending respiratory failure. The characteristics of bronchiolitis are described in Table 21-2.

Infants with respiratory distress usually are hospitalized. Treatment is supportive and includes administration of humidified oxygen to relieve hypoxia. Elevation of the head facilitates respiratory movements and avoids airway compression. Handling is kept at a minimum to avoid tiring. Because the infection is viral, antibiotics are not effective and are given only for a secondary bacterial infection. Dehydration may occur as the result of increased insensible water losses because of the rapid respiratory rate and feeding difficulties, and measures to ensure adequate hydration are needed. Recovery usually begins after the first 48 to 72 hours and usually is rapid and complete.

Signs of Impending Respiratory Failure

Respiratory problems of infants and small children often begin suddenly, and recovery usually is rapid and complete. Children are at risk for the development of airway obstruction and respiratory failure resulting from obstructive disorders or lung infection. The child with epiglottitis is at risk for airway obstruction. The child with bronchiolitis is at risk for respiratory failure resulting from impaired gas exchange. Children with impending respiratory failure due to airway or lung disease have rapid breathing, exaggerated use of the accessory muscles, retractions that are more pronounced in the child than in the adult because of a more compliant chest, nasal flaring, and grunting during expiration.[64] The signs and symptoms of impending respiratory failure are listed in Chart 21-1.

Respiratory failure can result from central nervous system conditions such as narcotic overdose or brain tumor that cause a decreased ventilatory drive and hypoventilation.

CHART 21-1

Signs of Respiratory Distress and Impending Respiratory Failure in the Infant and Small Child

- Severe increase in respiratory effort, including severe retractions or grunting, decreased chest movement
- Cyanosis that is not relieved by administration of oxygen (40%)
- Heart rate of 150 per minute or greater and increasing
- Bradycardia
- Very rapid breathing (rate 60 per minute in the newborn to 6 months or above 30 per minute in children 6 months to 2 years)
- Very depressed breathing (rate 20 per minute or below)
- Retractions of the supraclavicular area, sternum, epigastrium, and intercostal spaces
- Extreme anxiety and agitation
- Fatigue
- Decreased level of consciousness

In summary, although other body systems are physiologically ready for extrauterine life as early as 25 weeks of gestation, the lungs take longer. It is also during this period that type II alveolar cells, which produce surfactant, begin to function. Lung development is incomplete at birth; an infant is born with only one-eighth to one-sixth the adult number of alveoli. Alveoli continue to be formed during early childhood, reaching the adult number of 300 million alveoli by 5 to 6 years of age.

Most lung diseases in infants and children produce a decrease in lung compliance with manifestations of restrictive lung disease. They breathe at faster rates and their respiratory excursions are shallow. An *expiratory grunt* is common as the child tries to raise the functional residual capacity by closing the glottis at the end of expiration. *Nasal flaring* helps reduce the nasal resistance and maintain airway patency. *Inspiratory retractions,* or pulling in of the soft tissue surrounding the cartilaginous and bony thorax, is often observed with airway obstruction in infants and small children. Obstruction of the extrathoracic airways often produces turbulence of airflow and an audible inspiratory crowing sound called *stridor,* and obstruction of the intrathoracic airways produces an audible expiratory wheezing or whistling sound.

The neonatal period is one of transition from placental dependence to air breathing. Respiratory disorders develop in infants who are born prematurely or have other problems that impair this transition. RDS is one of the most common causes of respiratory disease in premature infants. In these infants, pulmonary immaturity,

together with surfactant deficiency, lead to decreased lung compliance, atelectasis, hypoxia, decreased pulmonary perfusion, and formation of a hyaline membrane. BPD is a chronic pulmonary disease that develops in premature infants who were treated with mechanical ventilation.

Acute respiratory infections are the most common cause of illness in infancy and childhood. Because of the small size of the airway of infants and children, infections that may cause only a sore throat and hoarseness in the adult may produce serious obstruction in the child. Among the respiratory tract infections that affect small children are croup, epiglottitis, and bronchiolitis. Croup or acute laryngotracheobronchitis is a viral infection that affects the larynx, trachea, and bronchi. Epiglottitis is a life-threatening supraglottic infection that may cause airway obstruction and asphyxia. Acute bronchiolitis is a viral infection of the lower airways, most commonly caused by the respiratory syncytial virus.

Review Exercises

It is influenza season, and although you had a flu shot last year, you have not had one this year. Imagine yourself experiencing the abrupt onset of fever, chills, malaise, muscle aching, and nasal stuffiness.

A. Which of these symptoms would lead you to believe you are coming down with the flu?
B. Because you have to miss class, you decide to go to the student health center and obtain an antibiotic. After being seen by the health professional, you are told that antibiotics are ineffective against the influenza virus, and you are instructed not to attend classes but instead go home, take acetaminophen for your fever, go to bed and stay warm, and drink a lot of fluid. Explain the rationale for each of these recommendations.
C. Explain why last year's flu shot did not protect you during this year's flu season. There is current concern about the possibility of an influenza pandemic such as occurred during the 1917–1918 season. What is the rationale for this concern?

A nurse working in an extended care facility finds out that the tuberculin skin test she had is positive. The test she had done a year ago was negative.

A. Explain what this means in terms of recency of exposure to *M. tuberculosis*. Does she have tuberculosis?

Bacterial (*e.g., Streptococcus pneumoniae*) pneumonia is commonly manifested by a cough productive of sputum, whereas with atypical (*e.g., Mycoplasma pneumoniae*) pneumonia, the cough is usually nonproductive or absent.

A. Explain.

A 4-month-old infant is admitted to the pediatric intensive care unit with a diagnosis of bronchiolitis. The infant is tachypneic, with wheezing, nasal flaring, and retractions of the lower sternum and intercostal spaces during inspiration.

A. What is the usual pathogen in bronchiolitis? Would this infection be treated with an antibiotic?
B. Explain the physiologic mechanism involved in the retraction of the lower sternum and intercostal spaces during inspiration.
C. What would be the signs of impending respiratory failure in this infant?

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