Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

23

Pneumonia

ETIOLOGY AND PATHOGENESIS, 298
Bacteria, 299
Viruses, 300
Mycoplasma, 300
PATHOLOGY, 301
PATHOPHYSIOLOGY, 301
CLINICAL FEATURES, 302
DIAGNOSTIC APPROACH, 303
THERAPEUTIC APPROACH: GENERAL PRINCIPLES AND ANTIBIOTIC SUSCEPTIBILITY, 306
INITIAL MANAGEMENT STRATEGIES BASED ON CLINICAL SETTING OF PNEUMONIA, 307
Community-Acquired Pneumonia, 307
Nosocomial (Hospital-Acquired) Pneumonia, 309
INTRATHORACIC COMPLICATIONS OF PNEUMONIA, 310
Lung Abscess, 310
Empyema, 310
RESPIRATORY INFECTIONS ASSOCIATED WITH BIOTERRORISM, 310
Anthrax, 311
Plague, 311
Tularemia, 311

By nearly any criteria, pneumonia (infection of the pulmonary parenchyma) must be considered one of the most important categories of disease affecting the respiratory system. Of note:

- Pneumonia is extraordinarily common; it is the most common reason for hospital admission in the United States other than women giving birth.
- Mortality is higher with an admitting diagnosis of pneumonia for adults 65 years of age in the United States than for any of the other top 10 admitting diagnoses.
- In 2011, pneumonia had an aggregate cost of nearly $10.6 billion for 1.1 million hospital stays in the United States.
- It is the world's leading cause of death among children under 5 years of age, and it is the most common reason for children to be hospitalized in the United States.
- Worldwide, pneumonia afflicts an estimated 450 million people per year and results in 4 million deaths.

It is no wonder that Sir William Osler referred to pneumonia as "the captain of the men of death," particularly as he spoke before the era of effective antibiotic therapy. For many types of pneumonia, medical therapy with antibiotics (along with supportive care) has great impact on the duration and outcome of the illness. Because of the effectiveness of treatment, the diseases discussed in this chapter are typically gratifying to treat for all involved medical personnel. Unfortunately, the emerging trend during the past 20 years has been the acquisition of antibiotic resistance by some of the

Abstract

By nearly any criteria, pneumonia (infection of the pulmonary parenchyma) must be considered one of the most important categories of disease affecting the respiratory system. This chapter is organized primarily as a general discussion of the clinical problem of pneumonia. As appropriate, the focus on individual etiologic agents highlights some characteristic features of each that are particularly useful to the physician. Also covered is a commonly used categorization of pneumonia based on the clinical setting: community-acquired versus nosocomial (hospital-acquired) pneumonia. In current clinical practice, the approach to evaluation and management of these two types of pneumonia is often quite different. The chapter concludes with a brief discussion of several infections that were uncommon or primarily of historical interest until recently, as the threat of bioterrorism emerged. In addition to reviewing inhalational anthrax, the chapter briefly describes two other organisms considered to be of concern as potential weapons of bioterrorism: *Yersinia pestis* (the cause of plague) and *Francisella tularensis* (the cause of tularemia).

Keywords

Pneumonia
Streptococcus pneumoniae
Mycoplasma
Chlamydophila
Lung abscess
Empyema, pleural
Anthrax
Plague
Tularemia

organisms causing pneumonia, and treatment of pneumonia has had to evolve to keep pace.

Although many of the specific agents causing pneumonia are considered here, this chapter is organized primarily as a general discussion of the clinical problem of pneumonia. As appropriate, the focus on individual etiologic agents highlights some characteristic features of each that are particularly useful to the physician. Also covered is a commonly used categorization of pneumonia based on the clinical setting: community-acquired versus nosocomial (hospital-acquired) pneumonia. In current clinical practice, the approach to evaluation and management of these two types of pneumonia is often quite different.

The chapter concludes with a brief discussion of several infections that were uncommon or primarily of historical interest until recently, as the threat of bioterrorism emerged. In addition to reviewing inhalational anthrax, the chapter briefly describes two other organisms considered to be of concern as potential weapons of bioterrorism: *Yersinia pestis* (the cause of plague) and *Francisella tularensis* (the cause of tularemia).

ETIOLOGY AND PATHOGENESIS

The host defenses of the lung are constantly challenged by a variety of organisms, including both viruses and bacteria (see Chapter 22). Viruses in particular are likely to avoid or overwhelm some of the upper respiratory tract defenses, causing a transient, relatively mild, clinical illness with symptoms limited to the upper respiratory tract. When host defense mechanisms of the upper and lower respiratory tracts are overwhelmed, microorganisms may establish residence, proliferate, and cause a frank infectious process within the pulmonary parenchyma. With particularly virulent organisms, no major impairment of host defense mechanisms is needed; pneumonia may occur even in normal and otherwise healthy individuals. At the other extreme, if host defense mechanisms are quite impaired, microorganisms that are not particularly virulent and are unlikely to cause disease in a healthy host may produce a life-threatening pneumonia.

Common contributing factors for pneumonia in the immunocompetent host are:

1. Viral upper respiratory tract infection
2. Ethanol abuse
3. Cigarette smoking
4. Heart failure
5. Chronic obstructive pulmonary disease

In practice, several factors frequently cause enough impairment of host defenses to contribute to the development of pneumonia, even though individuals with such impairment are not considered "immunosuppressed." Viral upper respiratory tract infections, ethanol abuse, cigarette smoking, heart failure, and preexisting chronic obstructive pulmonary disease (COPD) are a few of the contributing factors. More severe impairment of host defenses is caused by diseases associated with immunosuppression (e.g., advanced AIDS), various underlying malignancies (particularly leukemia and lymphoma), and the use of corticosteroids and other immunosuppressive drugs. In these cases associated with impairment of host defenses, individuals are susceptible to both bacterial and more unusual nonbacterial infections (see Chapters 24 to 26).

Microorganisms, especially bacteria, find their way to the lower respiratory tract in two major ways. The first is by inhalation, whereby organisms are usually carried in small droplet particles inhaled into the tracheobronchial tree. The second is by aspiration, whereby secretions from the oropharynx pass through the larynx and into the tracheobronchial tree. Aspiration is usually thought of as a process occurring in individuals unable to protect their airways from secretions by glottic closure and coughing. Although clinically significant aspiration is more likely to occur in such individuals, everyone is subject to aspirating small amounts of oropharyngeal secretions, particularly during sleep. Defense mechanisms seem able to cope with this nightly onslaught of bacteria, and frequent bouts of aspiration pneumonia are not experienced.

Less commonly, bacteria reach the pulmonary parenchyma through the bloodstream rather than by the airways. This route is important for the spread of certain organisms, particularly *Staphylococcus*. When pneumonia results in this way from bacteremia, the

implication is that a distant primary source of bacterial infection is present or that bacteria were introduced directly into the bloodstream (e.g., with intravenous drug use).

Many individual infectious agents are associated with the development of pneumonia. The frequency with which each agent is involved is difficult to assess and depends to a large extent on the specific population studied. The largest single category of agents is probably bacteria. The other two major categories are viruses and *Mycoplasma*. Of the bacteria, the organism most frequently associated with pneumonia is *Streptococcus pneumoniae*; in common parlance, it is often called *pneumococcus*. It has been estimated that in adults, approximately one-half of all pneumonias serious enough to require hospitalization are caused by *S. pneumoniae.*

Streptococcus pneumoniae (pneumococcus) is the most common cause of bacterial pneumonia. The polysaccharide capsule is an important factor in its virulence.

Bacteria

S. pneumoniae, a normal inhabitant of the oropharynx in a large proportion of adults, is a Gram-positive coccus typically seen in pairs, or diplococci. Pneumococcal pneumonia is commonly acquired in the community (i.e., in nonhospitalized patients) and frequently occurs following a viral upper respiratory tract infection. The organism has a polysaccharide capsule that interferes with immune recognition and phagocytosis, and therefore is an important factor in its virulence. There are many different antigenic types of capsular polysaccharide, and for host defense cells to phagocytize the organism, the antibody against the particular capsular type must be present. Antibodies contributing in this way to the phagocytic process are called *opsonins* (see Chapter 22).

Staphylococcus aureus is another gram-positive coccus, but usually appears in clusters when examined microscopically. Three major settings in which this organism is seen as a cause of pneumonia are (1) as a secondary complication of respiratory tract infection with the influenza virus; (2) in the hospitalized patient, who often has some impairment of host defense mechanisms and whose oropharynx has been colonized by *Staphylococcus*; and (3) as a complication of widespread dissemination of staphylococcal organisms through the bloodstream.

Factors predisposing to oropharyngeal colonization and pneumonia with gram-negative organisms are:

1. Hospitalization or residence in a chronic care facility
2. Underlying disease and compromised host defenses
3. Recent antibiotic therapy

A variety of gram-negative organisms are potential causes of pneumonia, but only a few of the most important examples from this group of organisms are mentioned here. *Haemophilus influenzae*, a small coccobacillary gram-negative organism, is often found in the nasopharynx of normal individuals and in the lower airways of patients with COPD. It can cause pneumonia in children and adults—the latter often with underlying COPD as a predisposing factor. *Klebsiella pneumoniae*, a relatively large gram-negative rod normally found in the gastrointestinal tract, has been best described as a cause of pneumonia in the setting of underlying alcoholism. *Pseudomonas aeruginosa*, found in a variety of environmental sources (including the hospital environment), is seen primarily in patients who are debilitated, hospitalized, and often previously treated with antibiotics. *P. aeruginosa* is also a very common cause of respiratory tract infections in patients with underlying bronchiectasis or cystic fibrosis.

The bacterial flora normally present in the mouth are potential etiologic agents in the development of pneumonia. A multitude of organisms (both gram-positive and gram-negative) that favor or require anaerobic conditions for growth are the major organisms comprising mouth flora. The most common predisposing factor for anaerobic pneumonia is the aspiration of secretions from the oropharynx into the tracheobronchial tree. Patients with impaired consciousness (e.g., as a result of coma, alcohol or drug ingestion, or seizures) and those with difficulty swallowing (e.g., as a result of stroke or diseases causing muscle weakness) are prone to aspirate and are at greatest risk for pneumonia caused by anaerobic or mixed mouth organisms. In addition, patients with poor dentition or gum disease are more likely to develop aspiration pneumonia because of the larger burden of organisms in their oral cavity.

Anaerobes normally found in the oropharynx are the usual cause of aspiration pneumonia.

In some settings, such as prolonged hospitalization or recent use of antibiotics, the type of bacteria residing in the oropharynx may change. Specifically, aerobic

gram-negative bacilli and *S. aureus* are more likely to colonize the oropharynx, and any subsequent pneumonia resulting from aspiration of oropharyngeal contents may include these aerobic organisms as part of the process.

The two final types of bacteria mentioned here are more recent additions to the list of etiologic agents. The first of these organisms, *Legionella pneumophila*, was identified as the cause of a mysterious outbreak of pneumonia in 1976 affecting American Legion members at a convention in Philadelphia. Since then it has been recognized as an important cause of pneumonia occurring in epidemics, as well as in isolated sporadic cases, and seems to affect both previously healthy individuals and those with prior impairment of respiratory defense mechanisms. Retrospectively, several prior outbreaks of unexplained pneumonia have been shown to be due to this organism. Although the organism technically is a gram-negative bacillus, it is poorly visualized by conventional staining methods.

The other organism, *Chlamydophila pneumoniae*, has been recognized in epidemiologic studies as the cause of approximately 5% to 10% of cases of pneumonia. It appears related to gram-negative bacteria, and for part of its life cycle it is an obligate intracellular parasite. Diagnosis is rarely made clinically because of the lack of distinguishing clinical and radiographic features, and the organism is not readily cultured. As a result, serologic studies serve as the primary means of diagnosis, although they are infrequently obtained and may be difficult to interpret.

Many other types of bacteria can cause pneumonia. Because all of them cannot be covered in this chapter, the interested reader should consult some of the more detailed publications listed in the references at the end of this chapter.

Viruses

Although viruses are extremely common causes of upper respiratory tract infections, they are diagnosed relatively infrequently as a cause of frank pneumonia, except in children. In adults, the influenza virus is the most commonly diagnosed agent. The 2010 H1N1 influenza pandemic fortunately caused fewer deaths than originally anticipated and raised the profile of best practices for prevention, diagnosis, and treatment of this virus. In contrast, the 1918 influenza pandemic is estimated to have resulted in 50 to 100 million deaths, or 3% to 5% of the world's population.

Outbreaks of pneumonia caused by adenovirus also are well described, particularly among military recruits. A relatively rare cause of a fulminant and often lethal pneumonia was described in the southwest United States, but cases in other locations have also been recognized. Species of *Hantavirus,* the genus of viruses responsible for this pneumonia, are found in rodents and were previously described as a cause of fever, hemorrhage, and acute renal failure in other parts of the world.

Several other viruses have caused limited epidemics of severe viral pneumonia in recent years. An outbreak of a novel, highly contagious, and highly lethal pneumonia was reported in 2003 in East Asia and Canada. The outbreak, termed *severe acute respiratory syndrome* (SARS), was attributed to a novel coronavirus that may have evolved from a type normally found in the civet (a weasel-like mammal found in Chinese markets). In 2012, *Middle East respiratory syndrome* (MERS) coronavirus caused an outbreak of severe pneumonia with a nearly 75% mortality rate. The causative agent is related to a virus that normally infects camels, and most cases have been traced to initial exposures in the Arabian Peninsula.

Mycoplasma

Mycoplasma appears to be a class of organisms that is intermediate between viruses and bacteria. Unlike bacteria, they have no rigid cell wall. Unlike viruses, they do not require the intracellular machinery of a host cell to replicate and are capable of free-living growth. Similar in size to large viruses, mycoplasmas are the smallest fully free-living organisms that have been identified thus far. These organisms are now recognized as

a common cause of pneumonia, and are perhaps responsible for a minimum of 10% to 20% of all cases. Mycoplasmal pneumonia occurs most frequently in young adults but is not limited to this age group. The pneumonia is generally acquired in the community—that is, by previously healthy, non-hospitalized individuals—and may occur in either isolated cases or localized outbreaks.

Mycoplasma, the smallest known free-living organism, is a frequent cause of pneumonia in young adults.

PATHOLOGY

The pathologic process common to all pneumonias is infection and inflammation of the distal pulmonary parenchyma. An influx of polymorphonuclear leukocytes (PMNs), edema fluid, erythrocytes, mononuclear cells, and fibrin develops to a variable extent in all cases. Bacterial pneumonias in particular are characterized by an exuberant outpouring of PMNs into alveolar spaces as they attempt to limit proliferation of the invading bacteria.

Individual types of pneumonia may differ in exact location and mode of spread of the infection. In the past, a distinction was often made between pneumonias that follow a "lobar" distribution, those that behave more like a "bronchopneumonia," and those with the pattern of an "interstitial pneumonia." However, these distinctions are often difficult to make because individual cases of pneumonia frequently do not adhere to any one particular pattern, but have mixtures of the three patterns in varying proportions. Given this limitation, a brief mention of the three major types follows.

Lobar Pneumonia. Lobar pneumonia has classically been described as a process not limited to segmental boundaries but rather tending to spread throughout an entire lobe of the lung. Spread of the infection is believed to occur from alveolus to alveolus and from acinus to acinus through interalveolar pores known as the *pores of Kohn*. The classic example of a lobar pneumonia is that due to *S. pneumoniae*, although many cases of pneumonia documented as being due to pneumococcus do not necessarily follow this typical pattern.

Bronchopneumonia. In bronchopneumonia, distal airway inflammation is prominent along with alveolar disease, and spread of the infection and the inflammatory process tends to occur through airways rather than through adjacent alveoli and acini. Whereas lobar pneumonias appear as dense consolidations involving part or all of a lobe, bronchopneumonias are more patchy in distribution, depending on where spread by airways has occurred. Many bacteria, such as staphylococci and a variety of gram-negative bacilli, may produce this patchy pattern.

Interstitial Pneumonia. Interstitial pneumonias are characterized by an inflammatory process within the interstitial walls rather than alveolar spaces. Although viral pneumonias classically start as interstitial pneumonias, severe cases generally show extension of the inflammatory process to alveolar spaces as well.

In some cases of pneumonia, the organisms are not highly destructive to lung tissue even though an exuberant inflammatory process may be seen. Pneumococcal pneumonia classically (although not always) behaves in this way, and the healing process is associated with restoration of relatively normal parenchymal architecture. In other cases, when the organisms are more destructive, tissue necrosis may occur, with resulting cavity formation or scarring of the parenchyma. Many cases of staphylococcal and anaerobic pneumonias follow this more destructive course.

PATHOPHYSIOLOGY

Infections of the pulmonary parenchyma produce their clinical sequelae not only by altering the normal functioning of the lung parenchyma but also by inducing a more generalized systemic response to invading microorganisms. The major pathophysiologic

Pneumonia commonly results in ventilation-perfusion mismatch (with or without shunting) and hypoxemia.

consequence of inflammation and infection involving the distal air spaces is decreased ventilation to affected areas. If perfusion is relatively maintained, as it often is because of the vasodilatory effects of inflammatory mediators, ventilation-perfusion mismatch results, with low ventilation-perfusion ratios in diseased regions. When alveoli are totally filled with inflammatory exudate, there may be no ventilation to these regions, and extreme ventilation-perfusion inequality (i.e., shunt) results.

Ventilation-perfusion inequality generally manifests as hypoxemia. Although shunt may explain part of the hypoxemia, ventilation-perfusion mismatch with areas of low ventilation-perfusion ratio is usually a more important factor. Carbon dioxide retention is not a feature of pneumonia unless the patient already has an extremely limited reserve, especially from underlying COPD. In fact, patients with pneumonia frequently hyperventilate and have a P_{CO_2} less than 40 mm Hg.

The systemic response to pneumonia is not unique but rather is a reflection of the body's response to serious infection. Perhaps the most apparent aspects of this response are fever, an outpouring of PMNs into the circulation (particularly with bacterial pneumonia), and often a "toxic" appearance of the patient. These indirect systemic responses can be clues that an infectious process is the cause of a new pulmonary infiltrate.

CLINICAL FEATURES

In many ways the clinical manifestations of pneumonia are similar, even when different infectious agents are involved. In other ways, the presentations and manifestations are quite different. Although recognition of subtle clinical differences sometimes allows the astute clinician to suggest an etiologic diagnosis, methods for identifying a specific infectious agent are required for a definitive final diagnosis. However, in many cases, a specific agent cannot be clearly identified, and patients often are managed in an empirical way based on the setting in which they present.

Frequent clinical features in patients with pneumonia are:

1. Fever (with or without chills)
2. Cough (with or without sputum)
3. Dyspnea
4. Pleuritic chest pain
5. Crackles overlying affected region
6. Dullness, bronchial breath sounds, and egophony with frank consolidation
7. Polymorphonuclear leukocytosis

Perhaps the most important constellation of symptoms in almost any type of pneumonia consists of fever, cough, and often shortness of breath. The cough is nonproductive in some cases, particularly in pneumonias due to viruses or mycoplasma; in others, especially bacterial pneumonias, sputum production is a prominent feature. When the inflammatory process in the pulmonary parenchyma extends out to the pleural surface, the patient often reports pleuritic chest pain. If the fever is high and "spiking," patients frequently experience shaking chills associated with the rapid rise in body temperature.

Physical examination reflects the systemic response to infection and the ongoing inflammatory process in the lung. Patients often have tachycardia, tachypnea, and fever. Examination of the chest typically reveals crackles or rales overlying the region of the pneumonia. If dense consolidation is present and the bronchus supplying the area is patent, sound transmission is greatly increased through the consolidated pneumonic area. As a result, breath sounds may be increased and bronchial in quality, fremitus is increased, and egophony is present. The consolidated area is characteristically dull to percussion of the overlying chest wall. Examination of peripheral blood generally shows an increase in white blood cell count (leukocytosis). Especially in patients with bacterial pneumonia, the leukocytosis is composed primarily of PMNs, and a shift toward greater numbers of immature neutrophils such as band forms may be seen.

In pneumococcal pneumonia, the onset of the clinical illness often is relatively abrupt, with the sudden development of shaking chills and high fever. The cough may be productive of yellow, green, or blood-tinged (rusty-colored) sputum. Before the development of pneumonia, patients often have experienced a viral upper respiratory tract infection, which can be an important predisposing feature.

Mycoplasmal pneumonia, in contrast to pneumococcal pneumonia, characteristically has a somewhat slower, more insidious onset. Cough is a particularly prominent symptom,

but it often is non-productive. Fever is not as high, and shaking chills are uncommon. Young adults are the individuals most likely to have mycoplasmal pneumonia, although the disease is not limited to this age group.

Patients with either staphylococcal or gram-negative bacillary pneumonias are often quite ill. Frequently these patients have complex underlying medical problems and have already been hospitalized. Many have impaired defense mechanisms or have recently received antibiotics. Staphylococcal pneumonia classically may be seen as a secondary complication of influenza infection or as a result of dissemination of the organism through the bloodstream.

Pneumonia with anaerobic organisms generally occurs in patients with impaired consciousness or difficulty swallowing who cannot adequately protect the airway from aspiration of oropharyngeal secretions. Dentition often is poor, and patients frequently have gingivitis or periodontal abscesses. Clinical onset of the pneumonia tends to be gradual, and sputum may have a particularly foul odor, suggesting anaerobic infection. Successful culture of causative organisms may be difficult. While generally slow growing, anaerobic organisms can cause substantial tissue destruction, and necrosis of affected tissue and abscess formation are relatively common sequelae.

Pneumonia caused by *L. pneumophila*, commonly called *Legionnaires' disease*, can be seen as isolated cases or localized outbreaks. Otherwise healthy hosts may be affected, but patients with impaired respiratory defense mechanisms appear to be predisposed. Patients are often extremely ill, not only with respiratory compromise and even respiratory failure but also with nonrespiratory manifestations; specifically, gastrointestinal, central nervous system, hepatic, and renal abnormalities may accompany the pneumonia.

DIAGNOSTIC APPROACH

As with other disorders affecting the pulmonary parenchyma, the single most useful tool for assessing pneumonia at the macroscopic level is the chest radiograph in both posteroanterior and lateral views. The radiograph not only confirms the presence of a pneumonia but also shows the distribution and extent of disease and sometimes give clues about the nature of the etiologic agent. The classic pattern for *S. pneumoniae* (pneumococcus) and *K. pneumoniae* is a lobar pneumonia (Fig. 23.1). Staphylococcal and many of the gram-negative pneumonias may be localized or extensive and often follow a patchy distribution (Fig. 23.2). *Mycoplasma* organisms can produce a variety of radiographic presentations, which are classically described as being more impressive than the clinical picture would suggest. Pneumonias caused by aspiration of oropharyngeal secretions characteristically involve the dependent regions of lung: the lower lobe in the upright patient or the posterior segment of the upper lobe or superior segment of the lower lobe in the supine patient (Fig. 23.3). *Legionella* pneumonia most commonly presents with a patchy or consolidated unilobar infiltrate, although all patterns have been described.

Chest radiographs also are useful for demonstrating the presence of pleural fluid, which frequently accompanies pneumonia, particularly of bacterial origin. The pleural fluid can be either thin and serous or thick and purulent; in the latter case, the term *empyema* is used (discussed later under Empyema).

Microscopic examination of sputum may play an important role in evaluating patients with pneumonia. However, the importance of obtaining a sputum specimen and using it as a guide to treatment, as opposed to treating the patient empirically without a sputum specimen, is an issue of substantial controversy. For patients who do not require hospitalization, most authorities now recommend basing initial treatment on clinical presentation, without substantial efforts at identifying a causative organism. In contrast, patients who are sick enough to be admitted to the hospital are still treated empirically, but attempts are made to identify the organism in order to further guide therapy. When

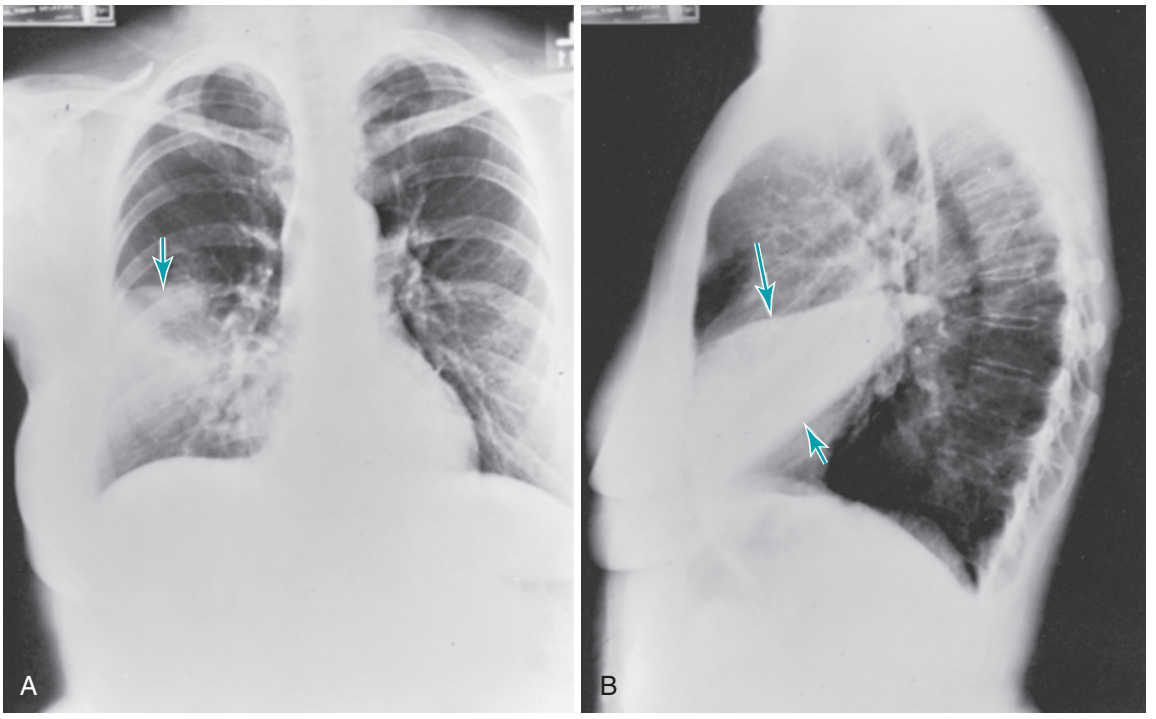

Figure 23.1. Posteroanterior **(A)** and lateral **(B)** chest radiographs show lobar pneumonia (probably caused by *Streptococcus pneumoniae*) affecting the right middle lobe. In **A**, the arrow points to a minor fissure, which defines the upper border of the middle lobe. In **B**, the long arrow points to a minor fissure, and the short arrow points to a major fissure.

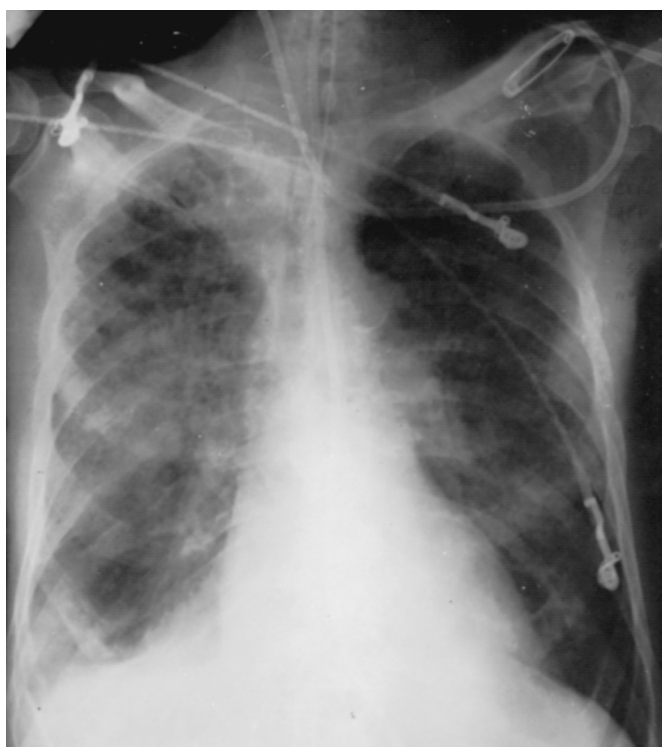

Figure 23.2. Chest radiograph of a patient with extensive gram-negative pneumonia. Note the patchy infiltrates throughout both lungs, which are more prominent on the right.

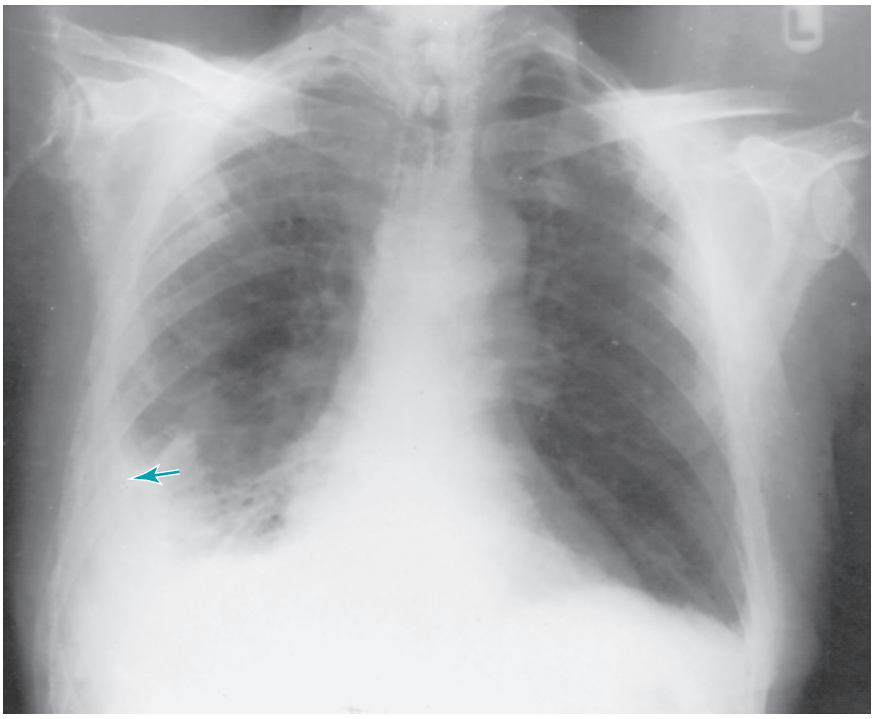

Figure 23.3. Chest radiograph of right lower lobe aspiration pneumonia. In addition to the infiltrate at the right base, note the loculated pleural effusion, which represents empyema complicating pneumonia. Arrow points to the edge of the loculated effusion. (Courtesy Dr. T. Scott Johnson.)

a sputum specimen is obtained, it is important to evaluate the quality of the specimen because a poor quality specimen may provide inadequate or inaccurate information. In an appropriate sputum specimen (i.e., one that contains few squamous epithelial cells picked up in transit through the oropharynx), inflammatory cells and bacteria can be seen.

In most bacterial pneumonias, large numbers of PMNs are seen in the sputum. In contrast, mycoplasmal and viral pneumonias have fewer PMNs and more mononuclear inflammatory cells. Pneumococcal, staphylococcal, and gram-negative bacillary pneumonias commonly demonstrate a relatively homogeneous population of the infecting bacteria. Anaerobic aspiration pneumonias, caused by a mixture of organisms from the oropharynx, show a mixed population of bacteria of many different morphologies. In Legionnaires' disease, the bacterium does not stain well with the usual Gram stain reagent and generally requires special stains to appreciate its presence. In mycoplasmal and viral pneumonia, the infecting agent is not visualized by light microscopy, and only the predominantly mononuclear cell inflammatory response is seen.

In conjunction with the initial Gram stain and microscopic examination of sputum, the specimen is cultured for bacteria. However, some bacteria are relatively difficult to grow, and in many if not most cases the initial Gram stain is just as important in making the etiologic diagnosis. Special culture media are available to facilitate the growth of *Legionella* species.

When sputum is not spontaneously expectorated by the patient, other methods for obtaining respiratory secretions (or even material directly from the lung parenchyma) may be necessary. Techniques that have been used—flexible bronchoscopy, needle aspiration of the lung, and occasionally surgical lung biopsy—are described in greater

detail in Chapter 3. Techniques for testing urine for the presence of antigens related to *S. pneumoniae* and *Legionella* (see below) are becoming increasingly useful.

Routine stains and cultures of sputum are not useful for three of the important causes of pneumonia: *Mycoplasma, Chlamydophila,* and *Legionella.* Sometimes the diagnosis can be confirmed by a variety of serologic techniques that demonstrate a rise in antibody titer against the organism, but these techniques provide a retrospective diagnosis and are not clinically useful. Several newer methods are seeing increasing clinical usefulness over time. For example, direct fluorescent antibody staining can be performed for *Legionella*, especially on tissue specimens, but more recent methods include culture on special supplemented media and a commonly used urinary antigen radioimmunoassay (only for certain *L. pneumophila* serotypes). Nucleic acid amplification methods, including polymerase chain reaction, are now widely used to detect *Mycoplasma, Chlamydophila*, and specific respiratory viruses, such as influenza or coronaviruses.

Functional assessment of patients with acute infectious pneumonia is usually limited to evaluating gas exchange. Arterial blood gas values characteristically demonstrate hypoxemia accompanied by normal or decreased P_{CO_2}, as well as a widened alveolar-arterial (A-a) oxygen gradient. Pulmonary function tests have little usefulness in this setting.

THERAPEUTIC APPROACH: GENERAL PRINCIPLES AND ANTIBIOTIC SUSCEPTIBILITY

The cornerstone of treatment of bacterial pneumonia is prompt, effective, antibiotic therapy directed at the infecting organism. However, because the causative organism often is not known when the pneumonia is first diagnosed and, in fact, frequently is not identified at any point during the clinical course, initial treatment strategies have been developed on the basis of the clinical setting (e.g., community-acquired vs. hospital-acquired pneumonia). These initial treatment strategies are outlined later under Initial Management Strategies Based on Clinical Setting of Pneumonia. If and when an organism is identified, the regimen may be changed to allow for more focused or more effective antibiotic coverage. Because knowledge of antibiotic susceptibility of specific organisms helps with understanding the rationale behind initial treatment strategies, this section first considers some of the general patterns of antibiotic susceptibility for the major organisms causing pneumonia.

In the case of pneumococcal pneumonia, penicillin has been the most appropriate agent traditionally, assuming the patient is not allergic to penicillin, although cases with various degrees of resistance to penicillin are encountered with increasing frequency. In addition, because penicillin is not effective against some of the other common causes of community-acquired pneumonia (e.g., *Mycoplasma pneumoniae, C. pneumoniae*), other classes of antibiotics with a broader spectrum against agents causing community-acquired pneumonia are typically used when antibiotics are initiated. They include macrolides (erythromycin or a derivative, such as azithromycin) and quinolones (e.g., moxifloxacin). When high-level resistance of pneumococcus to penicillin is found, either a quinolone or vancomycin is typically necessary. Intermediately resistant strains can often be treated with ceftriaxone.

Staphylococci generally produce penicillinase, which requires the use of a penicillinase-resistant semisynthetic derivative of penicillin, such as oxacillin or nafcillin. Many staphylococci are also resistant to these derivatives, in which case vancomycin is the antibiotic of choice. *H. influenzae* may be sensitive to ampicillin, but the high frequency of organisms resistant to this antibiotic generally justifies alternative coverage, such as a second- or third-generation cephalosporin, an extended-spectrum macrolide, trimethoprim-sulfamethoxazole, a quinolone, or a β-lactam/β-lactamase inhibitor

combination. Many of the other gram-negative bacillary pneumonias often display resistance to a variety of antibiotics. Aminoglycosides (e.g., gentamicin and tobramycin), third- or fourth-generation cephalosporins, quinolones, carbapenems (e.g., meropenem), or an extended-spectrum penicillin with a β-lactamase inhibitor (e.g., piperacillin/tazobactam) may be used initially while antibiotic sensitivity testing is performed. Pneumonia caused by anaerobes is treated most commonly with either penicillin or clindamycin. A macrolide or a quinolone is the antibiotic of choice for pneumonias caused by either *Legionella* or *Mycoplasma*.

No definitive forms of therapy are available for most viral pneumonias, although rapid advances in this field may lead to the development of more clinically useful therapeutic agents. The influenza vaccine (see Chapter 22) is effective in preventing influenza in the majority of individuals who receive it, whereas antiviral agents (amantadine or rimantadine for influenza A, a neuraminidase inhibitor, such as zanamivir or oseltamivir, for influenza A or B) may reduce the duration or severity of the illness if given soon after the onset of clinical symptoms.

Other modalities of therapy are mainly supportive. Chest physical therapy and other measures to assist the clearance of respiratory secretions are useful for some patients with pneumonia, particularly if neuromuscular disease or other factors impair the effectiveness of the patient's cough. If patients have inadequate gas exchange, as demonstrated by significant hypoxemia, administration of supplemental O_2 is beneficial. Occasionally, frank respiratory failure develops, and appropriate supportive measures are instituted (see Chapter 29).

Frequently used antibiotics for common pneumonias are:

1. *S. pneumoniae* (penicillin, first- or second-generation cephalosporin, macrolide, selected quinolones)
2. *Staphylococcus* (oxacillin, nafcillin, cefazolin, vancomycin)
3. *Haemophilus influenzae* (second- or third-generation cephalosporins, trimethoprim-sulfamethoxazole, quinolone, macrolide)
4. Gram-negative rods (aminoglycosides, third- or fourth-generation cephalosporins, carbapenems, extended-spectrum penicillin with β-lactamase inhibitor)
5. Anaerobes (penicillin, clindamycin)
6. *Mycoplasma* organisms (macrolide, quinolone)
7. *Legionella* (macrolide, quinolone)
8. *Chlamydophila pneumoniae* (tetracycline, macrolide)

INITIAL MANAGEMENT STRATEGIES BASED ON CLINICAL SETTING OF PNEUMONIA

During the past two decades, greater emphasis on the cost-effective use of medical resources has spurred development of algorithms and guidelines for the clinician approaching common clinical problems. Pneumonia is a particularly good example of an important clinical problem for which such management strategies have been developed, relating to both diagnostic evaluation and initiation of therapy. Separate strategies are being promulgated for two distinct groups of patients with pneumonia, depending on the setting where the pneumonia developed: community-acquired or nosocomial (hospital-acquired). Guidelines apply to patients who do not have a significant underlying impairment of systemic host defense mechanisms, such as patients with AIDS or those receiving immunosuppressive drugs or cancer chemotherapy.

Community-Acquired Pneumonia

Community-acquired pneumonia refers to pneumonia that develops in the community setting (i.e., in an individual not hospitalized). Although this category is not meant to include patients with significant impairment of systemic host defense mechanisms, it can include patients with other coexisting illnesses or risk factors that alter the profile of organisms likely to be responsible for pneumonia.

Surprisingly, the cause of community-acquired pneumonia is never identified in a high proportion of patients, estimated to be up to 50%. The likelihood of particular agents is believed to be influenced by a number of modifying factors: the presence of coexisting illness, recent treatment with antibiotics, residence in a nursing home, and the severity of illness at the initial presentation. One issue that has sparked controversy is whether an attempt should be made to identify a specific etiologic agent, using Gram stain and culture, in patients with community-acquired pneumonia, or whether empirical therapy should be used based on the patient's risk factors, clinical characteristics, and local bacterial resistance patterns. If a specific pathogen is identified, modification of

In community-acquired pneumonia, factors influencing the likelihood of certain organisms and, therefore, the therapeutic approach, include age, the presence of coexisting illness, and the severity of pneumonia at the initial presentation.

the initial antibiotic regimen is often appropriate, particularly to avoid an overly broad spectrum of coverage.

Table 23.1 summarizes the etiology and initial management of four broad subcategories of patients with community-acquired pneumonia. The first group comprises patients who do not have coexisting cardiopulmonary disease or other modifying risk factors, who have not used antibiotics in the previous 3 months, and who do not require hospitalization. The most common pathogens in this group of patients include *S. pneumoniae, M. pneumoniae, C. pneumoniae*, respiratory viruses, and in smokers, *H. influenzae*. The preferred therapeutic regimen is one of the advanced-generation macrolide antibiotics, such as azithromycin or clarithromycin, but this recommendation is subject to local differences in rates of bacterial resistance. For example, in some regions of the United States, up to 45% of *S. pneumoniae* isolates are resistant to macrolides.

The second group includes patients who have coexisting cardiopulmonary disease or other modifying risk factors but still can be treated in an outpatient setting. Important

Table 23.1

ETIOLOGY AND INITIAL MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA*

Patient Category	Common Organisms	Other Miscellaneous Organisms	Initial Therapy
Outpatient, no cardiopulmonary disease or other modifying risk factors	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* Respiratory viruses *H. influenzae* (in smokers)	*Legionella* *M. tuberculosis* Endemic fungi	Advanced-generation macrolide (e.g., azithromycin or clarithromycin) *OR* Doxycycline
Outpatient with cardiopulmonary disease and/or other modifying factors	*S. pneumoniae* *M. pneumoniae* *H. influenzae* Aerobic gram-negative bacilli Respiratory viruses Anaerobes *C. pneumoniae*	*M. catarrhalis* *Legionella* *M. tuberculosis* Endemic fungi	Oral quinolone (with activity against pneumococcus) *OR* β-Lactam plus macrolide
Hospitalized	*S. pneumoniae* *H. influenzae* Polymicrobial (including anaerobes) Aerobic gram-negative bacilli *Legionella* *C. pneumoniae* Respiratory viruses	*M. pneumoniae* *M. catarrhalis* *M. tuberculosis* Endemic fungi	Intravenous (IV) β-lactam plus IV or oral macrolide or doxycycline *OR* IV quinolone
Hospitalized, severe pneumonia	*S. pneumoniae* *Legionella* *H. influenzae* Aerobic gram-negative bacilli *M. pneumoniae* Respiratory viruses *S. aureus*	*M. tuberculosis* *C. pneumoniae* Endemic fungi	IV β-lactam plus either IV macrolide (azithromycin) or IV quinolone†

*Excludes patients with human immunodeficiency virus infection.
†If there is a high risk for *Pseudomonas*, adjust the regimen to include two antipseudomonal agents.
C. pneumoniae, Chlamydophila pneumoniae; H. influenzae, Haemophilus influenzae; M. catarrhalis, Moraxella catarrhalis; M. pneumoniae, Mycoplasma pneumoniae; M. tuberculosis, Mycobacterium tuberculosis; S. aureus, Staphylococcus aureus; S. pneumoniae, Streptococcus pneumoniae.
Modified from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.

comorbidities that place a patient in this category include chronic heart, lung, hepatic, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or drugs; or the use of antibiotics within the prior 3 months (in which case, antibiotics from a different class should be used). Again, local resistance patterns of *S. pneumoniae* should be taken into account, and residence in a nursing home should be considered a factor that increases the risk of pneumonia caused by a gram-negative organism. Poor dentition (leading to an increased burden of anaerobic organisms in the mouth), problems with swallowing, or impaired consciousness increase the risk of an anaerobic aspiration pneumonia. Recommended options for the management of this group have included either an oral quinolone (used as a single agent) or a β-lactam antibiotic (e.g., second- or third-generation cephalosporin) given in combination with a macrolide (particularly an advanced-generation macrolide, such as azithromycin or clarithromycin).

The third and fourth groups differ from the first two on the basis of severity of the pneumonia. The third group is defined by a need for hospitalization. The fourth group includes patients with the most severe disease, which necessitates admission to an intensive care unit (ICU). These patients still commonly have pneumonia caused by *S. pneumoniae* or the other organisms found in outpatients, but with the additional concern for gram-negative bacilli, *Legionella*, and sometimes *S. aureus*. Therapy for these patients is adjusted accordingly (see Table 23.1). Antibiotics, such as a quinolone or an advanced-generation macrolide, plus a β-lactam (particularly a third-generation cephalosporin), a carbapenem, or an extended-spectrum penicillin with β-lactamase inhibitor, are typically used in these settings, frequently in combination with vancomycin.

There are increasing data to suggest that adjunctive treatment with corticosteroids may be beneficial in many patients with severe pneumonia. However, the practice has not been uniformly adopted, and some data suggest that patients with pulmonary infection due to influenza or *Aspergillus* may have worse outcomes if corticosteroids are used.

A number of scoring systems have been developed to assess the need for hospitalization or ICU admission for an individual patient based upon the demographic characteristics and the severity of the illness at presentation. A detailed discussion of these algorithms is beyond the scope of this chapter, but references to the most common clinical prediction rules are provided.

Nosocomial (Hospital-Acquired) Pneumonia

In contrast to community-acquired pneumonia, nosocomial pneumonia is acquired by hospitalized patients, generally after more than 48 hours of hospitalization. Patients in ICUs, especially those receiving mechanical ventilation, are at particularly high risk for developing this category of pneumonia. Perhaps the most common problem leading to nosocomial pneumonia is colonization of the oropharynx by organisms not usually present in this site, which is followed by microaspiration of oropharyngeal secretions into the tracheobronchial tree. Patients at risk often have other underlying medical problems, have been receiving antibiotics, or have an endotracheal tube in their airway that bypasses some of the normal protective mechanisms of the respiratory tract. Gastric acid–reducing medications, particularly proton-pump inhibitors, have been implicated as a risk factor for nosocomial pneumonia in some studies. An increase in gastric pH allowing increased bacterial growth is the presumed mechanism.

Organisms of particular concern in nosocomial pneumonia include *Staphylococcus aureus*, gram-negative bacilli, and *Legionella*.

Organisms of particular concern in patients who develop hospital-acquired pneumonia are enteric gram-negative bacilli and *S. aureus*, but other organisms such as *Pseudomonas aeruginosa* and *Legionella* can be involved. Diagnostic evaluation is difficult and often complicated by the need to distinguish bacterial colonization of the tracheobronchial tree from true bacterial pneumonia. The clinical issues involved with diagnostic testing and optimal forms of therapy are beyond the scope of this discussion but can be found in the references at the end of this chapter.

INTRATHORACIC COMPLICATIONS OF PNEUMONIA

As part of the discussion of pneumonia, two specific intrathoracic complications of pneumonia—lung abscess and empyema—are briefly considered because they represent important clinical sequelae.

Lung Abscess

A lung abscess, like an abscess elsewhere, represents a localized collection of pus. In the lung, abscesses generally result from tissue destruction complicating a pneumonia. The abscess contents are primarily PMNs, often with collections of bacterial organisms. When antibiotics have been administered, organisms may no longer be culturable from the abscess cavity.

Anaerobic bacteria are the agents most frequently responsible for lung abscesses.

Etiologic agents associated with formation of a lung abscess are generally those bacteria that cause significant tissue necrosis. Most commonly, anaerobic organisms are responsible, suggesting that aspiration of oropharyngeal contents is the predisposing event. However, aerobic organisms, such as *Staphylococcus* or enteric gram-negative rods, can also cause significant tissue destruction with cavitation of a region of lung parenchyma and abscess formation.

Treatment of a lung abscess involves antibiotic therapy, often given for longer than for an uncomplicated pneumonia. Although abscesses elsewhere in the body are drained by surgical incision, lung abscesses generally drain through the tracheobronchial tree, and surgical intervention or placement of a drainage catheter is needed only rarely.

Empyema

When pneumonia extends to the pleural surface, the inflammatory process eventually may lead to empyema, another intrathoracic complication of pneumonia. The term *empyema* (or more properly, *empyema thoracis*) refers to pus in the pleural space. In its most florid form, an empyema represents thick, creamy, or yellow fluid within the pleural space. The fluid contains enormous numbers of leukocytes, primarily PMNs, often accompanied by bacterial organisms. With a true empyema or often even with other grossly inflammatory pleural effusions accompanying pneumonia (parapneumonic effusions), pleural inflammation can result in formation of localized pockets of fluid or substantial scarring and limited mobility of the underlying lung.

Several different bacterial organisms may be associated with development of an empyema. Anaerobes are particularly common, but staphylococci and other aerobic organisms are also potential causes. After an empyema has been documented, usually by thoracentesis and sampling of pleural fluid, drainage of the fluid is required. In many cases thoracoscopic surgery is performed to completely drain the pleural space. Alternative techniques are used in some specific clinical situations and can include open surgical procedures or placement of large-bore chest tubes with repeated instillation of fibrinolytic agents (e.g., alteplase and DNase) into the pleural space.

Adequate drainage of pleural fluid is critical in the management of empyema.

RESPIRATORY INFECTIONS ASSOCIATED WITH BIOTERRORISM

The magnitude of society's concerns about bioterrorism has increased abruptly in recent years. In 2001, recognition of cases of both cutaneous and inhalational anthrax contracted by handling mail containing anthrax spores in the United States illustrated all too vividly not only the danger posed by some previously uncommon biological agents but also the widespread fear elicited by the threat of bioterrorism. This section briefly discusses three biological agents with life-threatening effects that can be mediated by infection involving the respiratory system: *Bacillus anthracis, Yersinia pestis,* and *Francisella tularensis.*

Anthrax

Bacillus anthracis, a gram-positive spore-forming rod found in soil, causes infection in farm stock and wild animals. Human cases have occurred as a result of exposure to infected animals, contaminated animal products, and inhalation of aerosolized spores. The virulence and potential lethality of the organism are related to elaboration of a toxin that causes prominent edema, inhibits neutrophil function, and alters production of a number of cytokines. Whereas cutaneous anthrax results from spores introduced through a break in the skin, inhalational anthrax follows the inhalation of spores into alveolar spaces and the transport of viable spores via lymphatics to the mediastinal lymph nodes. Germination of the spores in the mediastinum is associated with toxin release and a hemorrhagic lymphadenitis and mediastinitis.

Clinically, patients with inhalational anthrax typically present with a flulike illness with symptoms of mild fever, myalgias, nonproductive cough, malaise, and chest discomfort. Several days later, they become acutely and severely ill with fever, dyspnea, cyanosis, septic shock, and often findings of meningitis. The most prominent abnormality on chest radiograph is mediastinal widening from hemorrhagic lymphadenitis and mediastinitis. Because viable spores are present in the mediastinum and not the alveoli, anthrax is generally not transmitted from person to person via droplet nuclei. Despite treatment with ciprofloxacin or doxycycline, mortality is extremely high after the onset of clinical illness, and public health guidelines have focused on prophylaxis (with either of these antibiotics) to prevent inhalational anthrax following confirmed or suspected exposure to aerosolized spores. An anthrax vaccine is available but requires a complex administration schedule and annual booster injections.

Inhalational anthrax characteristically produces a widened mediastinum on chest radiograph.

Plague

Despite its association with epidemics of devastating proportions, such as the Black Death of the 14th century, plague is now an uncommon disease. However, plague is one of the conditions thought to be of major concern as a possible weapon of bioterrorism. The causative organism, *Yersinia pestis*, a gram-negative rod transmitted by fleas from rodents to humans, is still endemic in many parts of the world, including the southwest and Pacific coastal regions of the United States, the former Soviet Union, and focused areas in Africa, Asia, and South America. Infection through the skin disseminates to regional lymph nodes, leading to the clinical syndrome of *bubonic plague*. Infection of the lungs *(pneumonic plague)* can occur either secondary to bacteremic spread from skin or lymph nodes or via airborne transmission of the organism from person to person. Pneumonic plague is highly contagious through aerosolization of the organisms during cough.

Pulmonary involvement is characterized by widespread bronchopneumonia that can have regions of homogeneous consolidation. Clinically, patients become acutely ill with high fever, malaise, myalgias, rigors, dyspnea, and cyanosis. Chest radiography shows widespread bronchopneumonia with a diffuse pattern that can resemble acute respiratory distress syndrome (ARDS). Mortality is high unless antibiotic treatment is initiated soon after the onset of symptoms. Streptomycin and doxycycline are the treatments of choice.

Tularemia

Tularemia is caused by *Francisella tularensis*, a gram-negative coccobacillary organism that infects small mammals and is transmitted to humans by insect vectors (e.g., ticks), exposure to contaminated animals, or the inhalation of aerosolized organisms. Although several different forms of clinical presentation may occur with tularemia, depending on the mechanism of transmission and the site of entry, pulmonary tularemia secondary to inhalation of *F. tularensis* is the primary concern for the use of this organism as a bioterrorist weapon.

Pulmonary tularemia is characterized by patchy inflammation and consolidation of the lung parenchyma, sometimes with the enlargement of hilar lymph nodes and the development of pleural effusions. Patients develop fever, chills, malaise, and headache. Chest radiography shows patchy consolidation that may be accompanied by hilar lymphadenopathy and pleural effusions. Treatment consists of streptomycin, and mortality is estimated to be approximately 35% without treatment.

REFERENCES

GENERAL ARTICLES

Bassi GL, Ferrer M, Marti JD, et al. Ventilator-associated pneumonia. *Semin Respir Crit Care Med*. 2014;35:469–481.

Dickson RP, Erb-Downward JR, Huffnagle GB. Towards an ecology of the lung: new conceptual models of pulmonary microbiology and pneumonia pathogenesis. *Lancet Respir Med*. 2014;2:238–246.

Haq IJ, Battersby AC, Eastham K, et al. Community acquired pneumonia in children. *BMJ*. 2017;356:j686.

Harris AM, Hicks LA, Qaseem A, et al. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med*. 2016;164:425–434.

Herzig SJ, Howell MD, Ngo LH, et al. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301:2120–2128.

Kalil AC, Metersky ML, Klompas M, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.

Lee JS, Giesler DL, Gellad WF, et al. Antibiotic therapy for adults hospitalized with community-acquired pneumonia: a systematic review. *JAMA*. 2016;315:593–602.

Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009;64(suppl 3):iii1–iii55.

Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72.

Mazur NI, Martinón-Torres F, Baraldi E, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *Lancet Respir Med*. 2015;3:888–900.

Mina MJ, Klugman KP. The role of influenza in the severity and transmission of respiratory bacterial disease. *Lancet Respir Med*. 2014;2:750–763.

Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med*. 2014;371:1619–1628.

Nair GB, Niederman MS. Ventilator-associated pneumonia: present understanding and ongoing debates. *Intensive Care Med*. 2015;41:34–48.

Niederman MS. In the clinic: community-acquired pneumonia. *Ann Intern Med*. 2015;163:ITC1–ITC17.

Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015;386:1097–1108.

Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*. 2011;365:518–526.

Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163:519–528.

Torres A, Lee N, Cilloniz C, et al. Laboratory diagnosis of pneumonia in the molecular age. *Eur Respir J*. 2016;48:1764–1778.

Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J*. 2017;50:pii1700582.

Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. *N Engl J Med*. 2014;370:543–551.

PNEUMONIA CAUSED BY SPECIFIC ORGANISMS

Arabi YM, Balkhy HH, Hayden FG, et al. Middle East respiratory syndrome. *N Engl J Med*. 2017;376:584–594.

Basarab M, Macrae MB, Curtis CM. Atypical pneumonia. *Curr Opin Pulm Med*. 2014;20:247–251.

Biondi E, McCulloh R, Alverson B, et al. Treatment of mycoplasma pneumonia: a systematic review. *Pediatrics*. 2014;133:1081–1090.

Burillo A, Bouza E. Chlamydophila pneumoniae. *Infect Dis Clin North Am*. 2010;24:61–71.

Cunha BA, Burillo A, Bouza E. Legionnaires' disease. *Lancet*. 2016;387:376–385.

Dockrell DH, Whyte MKB, Mitchell TJ. Pneumococcal pneumonia. Mechanisms of infection and resolution. *Chest*. 2012;142:482–491.

Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med*. 2001;344:1917–1928.

Kruger DH, Figueiredo LT, Song JW, et al. Hantaviruses—globally emerging pathogens. *J Clin Virol*. 2015;64:128–136.

Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344:665–671.
Peiris JS, Yuen KY, Osterhaus AD, et al. The severe acute respiratory syndrome. *N Engl J Med*. 2003;349:2431–2441.
Psallidas I, Corcoran JP, Rahman NM. Management of parapneumonic effusions and empyema. *Semin Respir Crit Care Med*. 2014;35:715–722.
Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. *Lancet*. 2011;377:1264–1275.
Sharma L, Losier A, Tolbert T, et al. Atypical pneumonia: updates on Legionella, Chlamydophila, and Mycoplasma pneumonia. *Clin Chest Med*. 2017;38:45–58.
van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet*. 2009;374:1543–1556.
Waterer GW. Diagnosing viral and atypical pathogens in the setting of community-acquired pneumonia. *Clin Chest Med*. 2017;38:21–28.
Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med*. 2010;362:1708–1719.
Wunderink RG. Other community respiratory viruses. *Clin Chest Med*. 2017;38:37–43.
Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet*. 2015;386:995–1007.

RESPIRATORY INFECTIONS ASSOCIATED WITH BIOTERRORISM

Adalja AA, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. *N Engl J Med*. 2015;372:954–962.
Bush LM, Abrams BH, Beall A, et al. Index case of fatal inhalational anthrax due to bioterrorism in the United States. *N Engl J Med*. 2001;345:1607–1610.
Prentice MB, Rahalison L. Plague. *Lancet*. 2007;369:1196–1207.
Sweeney DA, Hicks CW, Cui X, et al. Anthrax infection. *Am J Respir Crit Care Med*. 2011;184:1333–1341.