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.

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Pneumonia

By any of several criteria, pneumonia (infection of the pulmonary parenchyma) must be considered one of the most important categories of disease affecting the respiratory system. First, pneumonia is extraordinarily common, accounting for nearly 10% of admissions to many large general hospitals. Overall, it has been estimated that more than 5 million cases of pneumonia occur each year in the United States. Second, pneumonia is a significant cause of death. More than 80,000 Americans die of bacterial pneumonia each year, making it the sixth most common cause of death in the nation. 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 typically are gratifying to treat for all involved medical personnel. Unfortunately, the emerging trend during the past 15 years has been the acquisition of antibiotic resistance by some of the organisms causing pneumonia. Therefore, it has been necessary for the treatment of pneumonia to evolve in order to keep pace with patterns of antibiotic resistance.

Although many of the specific agents causing pneumonia are considered here, this chapter is organized primarily as a general discussion of the 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. According to current

clinical practice, the approach to evaluation and management of these two types of pneumonia often is quite different.

The chapter concludes with a brief discussion of several infections that were uncommon or primarily of historical interest until September 11, 2001. After the terrorist attacks on the World Trade Center and the Pentagon, the threat of bioterrorism became a reality when spores of *Bacillus anthracis* sent through the mail resulted in cases of cutaneous and inhalational anthrax. 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, both viruses and bacteria (see Chapter 22). Viruses in particular are likely to avoid or to overwhelm some of the defenses of the upper respiratory tract, 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, that is, unlikely to cause disease in a healthy host, may produce a life-threatening pneumonia.

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 are a few of the contributing factors. More severe impairment of host defenses is caused by diseases associated with immunosuppression (e.g., acquired immunodeficiency syndrome), by various underlying malignancies (particularly leukemia and lymphoma), and by use of corticosteroids and other immunosuppressive or cytotoxic drugs. In these cases associated with impairment of host defenses, individuals are susceptible to both bacterial and more unusual nonbacterial infections (see Chapters 24–26).

Contributing factors for pneumonia in the immunocompetent host are the following:
1. Viral upper respiratory tract infection
2. Ethanol abuse
3. Cigarette smoking
4. Heart failure
5. Chronic obstructive pulmonary disease

Microorganisms, especially bacteria, find their way to the lower respiratory tract in two major ways. The first is by inhalation, whereby organisms usually are carried in small droplet particles that are 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 usually is 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, for example, as a consequence of intravenous drug abuse.

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 probably is 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 often called the pneumococcus. It has been estimated that in adults approximately half of all pneumonias serious enough to require hospitalization are pneumococcal in origin.

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 seen in pairs or diplococci. Pneumococcal pneumonia is commonly acquired in the community (i.e., in nonhospitalized patients) and frequently occurs after a viral upper respiratory tract infection. The organism has a polysaccharide capsule that protects the bacteria from phagocytosis and therefore is an important factor in its virulence. There are many antigenic types of capsular polysaccharide, and in order for host defense cells to phagocytize the organism, 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.

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,* which is a small coccobacillary gram-negative organism, is often found in the nasopharynx of normal individuals and in the lower airways of patients with chronic obstructive lung disease. It can cause pneumonia in children and adults, the latter often with underlying chronic obstructive lung disease as a predisposing factor. *Klebsiella pneumoniae,* a relatively large gram-negative rod that normally is found in the gastrointestinal tract, has been best described as a cause of pneumonia in the setting of underlying alcoholism. *Pseudomonas aeruginosa,* which may be found in a variety of environmental sources (especially in the hospital environment), is seen primarily in patients who are debilitated, hospitalized, and, often, previously treated with antibiotics.

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

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

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 composing mouth flora. The most common predisposing factor for anaerobic pneumonia is aspiration of secretions from the oropharynx into the tracheobronchial tree. Patients with impaired consciousness (e.g., as a result of coma, alcohol ingestion, or seizures) and those with difficulty swallowing (e.g., as a result of diseases causing muscle weakness) are prone to aspirate and are at risk for pneumonia caused by anaerobic 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. In addition, it seems to affect both previously healthy individuals and those with prior impairment of respiratory defense mechanisms. In retrospect, several prior outbreaks of unexplained pneumonia have been shown to be due to this organism. Although the organism is a gram-negative bacillus, it stains very poorly and is generally not seen 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 is an obligate intracellular parasite that appears more related to gram-negative bacteria than to viruses, the category in which it previously had been placed. 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, which are not readily available, serve as the primary means of diagnosis.

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.

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, influenza virus is the most commonly diagnosed agent. Outbreaks of pneumonia caused by adenovirus also are well recognized, particularly in 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. The virus responsible for this pneumonia, called *hantavirus,* is found in rodents and previously was described as a cause of fever, hemorrhage, and acute renal failure in other parts of the world.

An outbreak of highly contagious and highly lethal pneumonia was reported in 2003 in East Asia and Canada. Termed *severe acute respiratory syndrome* (SARS), the outbreak 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).

MYCOPLASMA

Mycoplasma appears to be a class of organisms 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 free-living organisms that have yet been identified. These organisms now are recognized as a common cause of pneumonia, perhaps responsible for a minimum of 10% to 20% of all cases of pneumonia. 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, nonhospitalized individuals, and may occur either in isolated cases or in 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 is seen to a variable extent in all cases. The 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.

The individual types of pneumonia may differ in the 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 often are 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 recognized 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 of the other 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 the 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 the invading microorganisms. The major pathophysiologic consequence of inflammation and infection involving the distal air spaces is a decrease in ventilation to the affected areas. If perfusion is relatively maintained,

as it often is, ventilation-perfusion mismatch results, with low ventilation-perfusion ratios in the 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.

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

Ventilation-perfusion inequality generally manifests as hypoxemia. Although frank shunting may explain part of the hypoxemia, ventilation-perfusion mismatch with areas of low ventilation-perfusion ratio usually is 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 chronic obstructive lung disease. 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 play an equally if not more important role in the final diagnosis. However, in many cases, a specific agent cannot be clearly identified, and patients often are managed in an empiric way based on the setting in which they present.

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 those pneumonias caused by 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.

Frequent clinical features in patients with pneumonia are the following:
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 and bronchial breath sounds with frank consolidation
7. Polymorphonuclear leukocytosis

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, then sound transmission is greatly increased through the consolidated, pneumonic area. As a result, breath sounds may be 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 the peripheral blood generally shows an increase in the white blood count (leukocytosis). Especially in patients with bacterial pneumonia, the leukocytosis is composed primarily of PMNs, and a shift toward immature, younger neutrophils (i.e., bands) may be seen.

In pneumococcal pneumonia, the onset of the clinical illness often is relatively abrupt, with shaking chills and high fever. Cough may be productive of yellow, green, or blood-tinged (rusty-colored) sputum. Before the development of pneumonia, patients often experience a viral upper respiratory tract infection, which presumably is 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 nonproductive. 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 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 foul odor, suggesting anaerobic infection. Because the organisms are likely to cause substantial tissue destruction, 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 often are 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. The radiograph not only confirms the presence of a pneumonia; it also shows the distribution and extent of disease and sometimes gives 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, 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).

The chest radiograph is useful for demonstrating 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 in the Empyema section).

Microscopic examination of the sputum may play an important role in the evaluation of 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. Most authorities now recommend basing initial treatment on clinical presentation. In cases in which a sputum specimen is obtained, it is important to evaluate the quality of the specimen because a poor-quality specimen may provide inadequate or

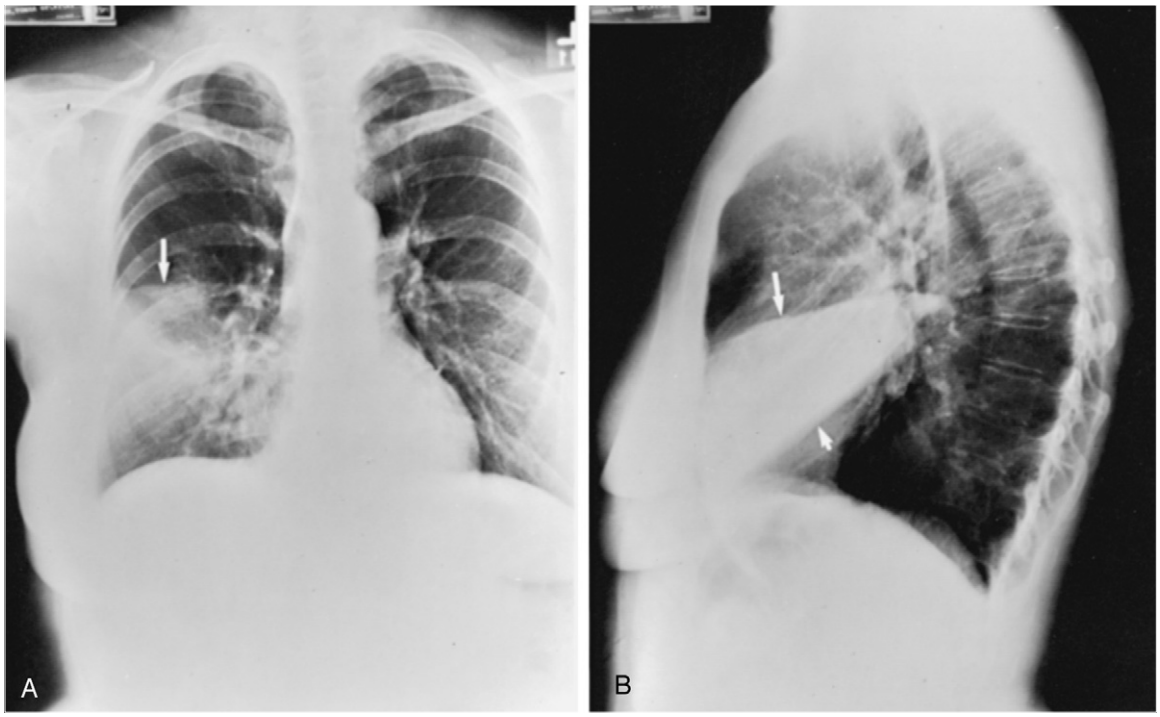

Figure 23-1. Posteroanterior *(A)* and lateral *(B)* chest radiographs show lobar pneumonia (probably caused by *Streptococcus pneumoniae)* affecting the right middle lobe. In **A,** arrow points to the minor fissure, which defines the upper border of the middle lobe. In **B,** long arrow points to the minor fissure, and short arrow points to the major fissure.

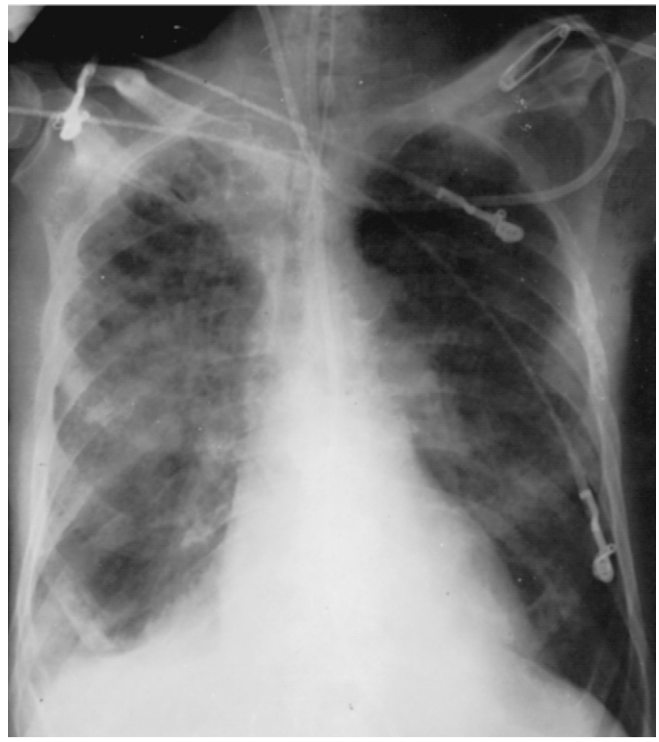

Figure 23-2. Chest radiograph of a patient with extensive gram-negative pneumonia. Note patchy infiltrates throughout both lungs, more prominent on the right.

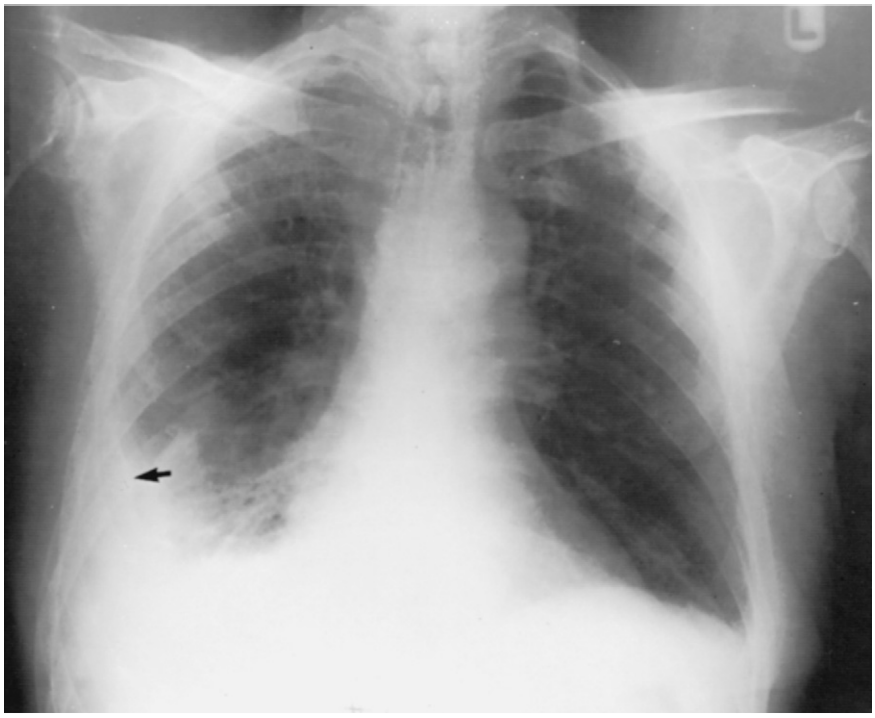

Figure 23-3. Chest radiograph of right lower lobe aspiration pneumonia. In addition to infiltrate at right base, note loculated pleural effusion, which represents empyema complicating pneumonia. Arrow points to edge of loculated effusion. (Courtesy Dr. T. Scott Johnson.)

inaccurate information. In a good sputum specimen (i.e., one that contains few squamous epithelial cells picked up in transit through the upper respiratory tract), 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 therefore is not seen with conventional staining techniques. 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. The techniques that have been used, including flexible bronchoscopy, needle aspiration of the lung, and occasionally surgical lung biopsy, are described in greater detail in Chapter 3.

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 useful clinically. 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). Polymerase chain reaction methods are being investigated for all three organisms and may have an important role in the future.

The functional assessment of patients with acute infectious pneumonia usually is limited to evaluation of gas exchange. Arterial blood gas values characteristically demonstrate hypoxemia, accompanied by a normal or decreased P_{CO_2}. Pulmonary function tests have little usefulness in this setting.

THERAPEUTIC APPROACH: GENERAL PRINCIPLES AND ANTIBIOTIC SUSCEPTIBILITY

The cornerstone of treatment of bacterial pneumonia is 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 in the section on 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.

Frequently used antibiotics for common pneumonias are the following:

1. *S. pneumoniae* (penicillin, 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)

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

Staphylococci generally produce penicillinase, which requires use of a penicillinase-resistant derivative of penicillin, such as oxacillin or nafcillin. Some 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, or a quinolone. 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 for most viral pneumonias are available, although rapid advances in this field may lead to development of more clinically useful therapeutic agents. 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 of the illness if given soon after onset of clinical symptoms.

Other modalities of therapy are mainly supportive. Chest physical therapy and other measures to assist 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).

INITIAL MANAGEMENT STRATEGIES BASED ON CLINICAL SETTING OF PNEUMONIA

During the past 2 decades, greater emphasis on the cost-effective use of medical resources has spurred the 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 in which the pneumonia developed, that is, *community-acquired pneumonia* and *nosocomial (hospital-acquired) pneumonia.* The patients in these categories to whom the guidelines apply do not have significant underlying impairment of systemic host defense mechanisms, such as patients with acquired immunodeficiency syndrome or those receiving immunosuppressive drugs or cancer chemotherapy.

COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia refers to pneumonia that develops in the community setting, that is, in an individual who is 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: presence of coexisting illness, recent treatment with antibiotics, residence in a nursing home, and severity of illness at 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 empiric therapy should be used based on the patient's risk factors and clinical characteristics. If a specific pathogen is identified, then modification of the initial antibiotic regimen often is appropriate, particularly to avoid an overly broad spectrum of coverage.

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

Four broad subcategories of patients with community-acquired pneumonia have been defined, as summarized in Table 23-1.

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 newer (advanced-generation) macrolide antibiotics, such as azithromycin or clarithromycin.

The second group includes patients who have coexisting cardiopulmonary disease or other modifying risk factors but who still can be treated in an outpatient setting. Important 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 use of antibiotics within the prior 3 months (in which case antibiotics from a different class should be used). 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 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 the severity of the pneumonia. The third group is defined by a need for hospitalization. The fourth group includes patients with the most severe disease, that which necessitates admission to an intensive care unit. These patients still commonly have pneumonia caused by *S. pneumoniae* or the other organisms found in outpatients but with additional concern for gram-negative bacilli, *Legionella,* and sometimes *Staphylococcus 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, typically are used in these settings, sometimes in combination with vancomycin.

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 intensive care units, especially those who are receiving mechanical ventilation, are at particularly high risk for developing this form 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.

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.

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 high risk for *Pseudomonas,* adjust 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.

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society: *Clin Infect Dis* 44(Suppl 2):S27–S72, 2007.

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 obtainable 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, also can cause significant tissue destruction, with excavation of a region of lung parenchyma and abscess formation.

Treatment of a lung abscess involves antibiotic therapy, often given for a more prolonged duration 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 a pneumonia extends to the pleural surface, the inflammatory process eventually may lead to empyema, another intrathoracic complication of pneumonia. The term *empyema* 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 frank 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 also are potential causes. After an empyema has been demonstrated, usually by thoracentesis and sampling of pleural fluid, drainage of the fluid is required. Most commonly, 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., streptokinase) into the pleural space.

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

RESPIRATORY INFECTIONS ASSOCIATED WITH BIOTERRORISM

The magnitude of society's concerns about bioterrorism changed abruptly after September 11, 2001, following the terrorist attacks on the World Trade Center and the Pentagon. Subsequent recognition of cases of both cutaneous and inhalational anthrax contracted by handling mail containing anthrax spores illustrated all too vividly not only the danger posed by some previously uncommon biologic agents but also the widespread

fear elicited by the threat of bioterrorism. This section briefly discusses three biologic 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 the 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 the production of a number of cytokines. Whereas cutaneous anthrax results from spores introduced through a break in the skin, inhalational anthrax follows inhalation of spores into alveolar spaces and transport of viable spores via lymphatics to mediastinal lymph nodes. Germination of the spores in the mediastinum is associated with toxin release and with 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, patients 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 the hemorrhagic lymphadenitis and mediastinitis. Because viable spores are present in the mediastinum and not in 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 fourteenth century, plague is now an uncommon disease in the United States, although it is endemic in some parts of the world. However, plague is one of the conditions thought to be of major concern as a possible weapon of bioterrorism. The causative organism is *Yersinia pestis*, a gram-negative rod that is transmitted by fleas from rodents to humans. 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 a widespread bronchopneumonia, which 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 the acute respiratory distress syndrome. Mortality is high unless antibiotic treatment is initiated soon after the onset of symptoms. Streptomycin and doxycycline are the agents 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 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 use of this organism as a bioterrorist weapon.

Pulmonary tularemia is characterized by patchy inflammation and consolidation of the lung parenchyma, sometimes with enlargement of hilar lymph nodes and 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 REVIEWS

American Thoracic Society and Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia, *Am J Respir Crit Care Med* 171:388–416, 2005.

Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ: Practice guidelines for the management of community-acquired pneumonia in adults, *Clin Infect Dis* 31:347–382, 2000.

Chastre J, Fagon J-Y: Ventilator-associated pneumonia, *Am J Respir Crit Care Med* 165:867–903, 2002.

Ewig S, Bauer T, Torres A: Nosocomial pneumonia, *Thorax* 57:366–371, 2002.

Fine MJ, Smith MA, Carson CA, et al: Prognosis and outcomes of patients with community-acquired pneumonia, *JAMA* 274:134–141, 1996.

Franquet T: Imaging of pneumonia: trends and algorithms, *Eur Respir J* 18:196–208, 2001.

Guthrie R: Community-acquired lower respiratory tract infections. Etiology and treatment, *Chest* 120:2021–2034, 2001.

Halm EA, Teirstein AS: Management of community-acquired pneumonia, *N Engl J Med* 347:2039–2045, 2002.

Hoare Z, Lim WS: Pneumonia: update on diagnosis and management, *BMJ* 332:1077–1079, 2006.

Kollef MH: Prevention of hospital-associated pneumonia and ventilator-associated pneumonia, *Crit Care Med* 32:1396–1405, 2004.

Leong JR, Huang DT: Ventilator-associated pneumonia, *Surg Clin North Am* 86:1409–1429, 2006.

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

Niederman MS: Recent advances in community-acquired pneumonia: inpatient and outpatient, *Chest* 131:1205–1215, 2007.

Porzecanski I, Bowton DL: Diagnosis and treatment of ventilator-associated pneumonia, *Chest* 130: 597–604, 2006.

PNEUMONIA CAUSED BY SPECIFIC ORGANISMS

Bartlett JG: Anaerobic bacterial infections of the lung, *Chest* 91:901–909, 1987.

File TM: Streptococcus pneumoniae and community-acquired pneumonia: a cause for concern, *Am J Med* 117(suppl 3A):39S–50S, 2004.

Gupta SK, Sarosi GA: The role of atypical pathogens in community-acquired pneumonia, *Med Clin North Am* 85:1349–1365, 2001.

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

Hammerschlag MR: Chlamydia pneumoniae and the lung, *Eur Respir J* 16:1001–1007, 2000.

Harwell JI, Brown RB: The drug-resistant pneumococcus. Clinical relevance, therapy, and prevention, *Chest* 117:530–541, 2000.

Kaye MG, Fox MJ, Bartlett JG, Braman SS, Glassroth J: The clinical spectrum of Staphylococcus aureus pulmonary infection, *Chest* 97:788–792, 1990.

Lednicky JA: Hantaviruses. A short review, *Arch Pathol Lab Med* 127:30–35, 2003.

Mansel JK, Rosenow EC III, Smith TF, Martin JW Jr: Mycoplasma pneumoniae pneumonia. *Chest* 95: 639–646, 1989.

Marik PE: Aspiration pneumonitis and aspiration pneumonia, *N Engl J Med* 344:665–671, 2001.

Peiris JS, Yuen KY, Osterhaus AD, Stöhr K: The severe acute respiratory syndrome, *N Engl J Med* 349:2431–2441, 2003.
Rose RM, Pinkston P, O'Donnell C, Jensen WA: Viral infection of the lower respiratory tract, *Clin Chest Med* 8:405–418, 1987.
Sanders CV, Kamholz SL, editors: Pneumococcal disease: a symposium in honor of Robert Austrian, MD, *Am J Med* 107(suppl):1S–90S, 1999.
Stout JE, Yu VL: Legionellosis, *N Engl J Med* 337:682–687, 1997.
Tuomanen EI, Austrian R, Masure HR: Pathogenesis of pneumococcal infection, *N Engl J Med* 332: 1280–1284, 1995.
Whitney CG, Farley MM, Hadler J, et al; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network: Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States, *N Engl J Med* 343:1917–1924, 2000.
Wilson R, Dowling RB: Pseudomonas aeruginosa and other related species, *Thorax* 53:213–219, 1998.
Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus: Update on avian influenza A (H5N1) virus infection in humans, *N Engl J Med* 358: 261–273, 2008.

RESPIRATORY INFECTIONS ASSOCIATED WITH BIOTERRORISM

Bellamy RJ, Freedman AR: Bioterrorism, *QJM* 94:227–234, 2001.
Borio L, Frank D, Mani V, et al: Death due to bioterrorism-related inhalational anthrax. Report of 2 patients, *JAMA* 286:2554–2559, 2001.
Bush LM, Abrams BH, Beall A, Johnson CC: Index case of fatal inhalational anthrax due to bioterrorism in the United States, *N Engl J Med* 345:1607–1610, 2001.
Centers for Disease Control: Recognition of illness associated with the intentional release of a biologic agent, *MMWR* 50:893–897, 2001.
Inglesby TV, O'Toole T, Henderson DA, et al; Working Group on Civilian Biodefense: Anthrax as a biological weapon, 2002. Updated recommendations for management, *JAMA* 287:2236–2252, 2002.
Mayer TA, Bersoff-Matcha S, Murphy C, et al: Clinical presentation of inhalational anthrax following bioterrorism exposure. Report of 2 surviving patients, *JAMA* 286:2549–2553, 2001.
Prentice MB, Rahalison L: Plague, *Lancet* 369:1196–1207, 2007.
Swartz MN: Recognition and management of anthrax—an update, *N Engl J Med* 345:1621–1626, 2001.