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97

OVERVIEW OF PNEUMONIA

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It is a useful distinction to separate pneumonias, which are infections of the lung parenchyma and thus distinct from infections limited to the trachea or large bronchi (Chapter 96), into those acquired in the community (community-acquired pneumonia) and those arising in institutional settings, with the second group being composed of hospital-acquired pneumonia, ventilator-associated pneumonia, and health care–associated pneumonia. These two major pneumonia categories are considered separately in this

chapter. Additional consideration should be given to pneumonia caused by recurrent aspiration of oropharyngeal contents.

The term *pneumonia* itself, however, includes other causes of inflammation of the lower respiratory air spaces, particularly the alveoli, such as acute or chronic eosinophilic pneumonia, cryptogenic organizing pneumonia, and usual interstitial pneumonia, all of which are presented in more detail elsewhere (Chapter 92).

COMMUNITY-ACQUIRED PNEUMONIA

DEFINITION

Community-acquired pneumonia includes cases of infectious pneumonia in patients living independently in the community. Patients who have been hospitalized for other reasons for less than 48 hours before the development of respiratory symptoms are also considered to have community-acquired pneumonia because it is likely that the inoculation had occurred before admission. However, patients who have previously been hospitalized for at least 2 days within the 90 days before infection; patients from nursing homes who received intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days; and patients from hemodialysis centers are considered to have health care–associated pneumonia and are therefore excluded from the case definition of community-acquired pneumonia. Patients contracting pneumonia more than 48 hours after the institution of endotracheal intubation and mechanical ventilation are also excluded inasmuch as they are considered to have ventilator-associated pneumonia. These distinctions are important because they help define the most likely infectious agents and hence strongly influence appropriate choices for the initial antibiotic therapy.

EPIDEMIOLOGY

More than 10 million cases of infectious pneumonia occur annually in the United States and result in more than 1 million hospitalizations. Pneumonia is a leading cause of death worldwide, the sixth leading cause of death in the United States, and the most common lethal infectious disease. The mortality rate associated with community-acquired pneumonia ranges from less than 5% in mildly ill outpatients to somewhat greater than 12% overall in patients who are admitted to a hospital. Mortality is even greater in patients who have severe invasive disease, which is often associated with bacteremia, and in elderly nursing home patients. Mortality from pneumonia can exceed 40% in patients who require management in the intensive care unit (ICU). It costs approximately $7000 to manage an uncomplicated case of pneumonia in the hospital, or about 20-fold more than treating it in the outpatient setting.

PATHOBIOLOGY

Aspiration of Oropharyngeal Contents

The most common mechanism by which the lung is inoculated with pathogenic organisms is through microaspiration of oropharyngeal contents, a process that occurs in otherwise healthy individuals during sleep (Chapter 94). Colonization of the oral pharynx with pathogenic organisms, such as *Streptococcus pneumoniae* (Chapter 297), can thereby lead to delivery of sufficient quantities of organisms to infect the lung. In contrast, gross aspiration normally occurs only in individuals with altered sensorium, depressed consciousness, abnormalities in protective cough or gag reflexes, or substantial gastroesophageal reflux. Gross aspiration, which can also deliver large numbers of anaerobic bacteria to the lower respiratory tract, is a major contributing factor to anaerobic lung infection and abscess formation (Chapter 90).

Inhalation of Aerosolized Droplets

The second most frequent mechanism of lung infection is the inhalation of small, suspended aerosolized droplets ranging in size from 0.5 to 1 μm that may contain microorganisms. In view of the limited number of organisms delivered in such a manner, only relatively aggressive pathogenic organisms such as *Mycobacterium tuberculosis* (Chapter 332), *Legionella pneumophila* (Chapter 322), *Yersinia pestis* (plague; Chapter 320), *Bacillus anthracis* (anthrax; Chapter 302), and some viral infections can be transmitted in this manner.

Blood Stream Infection

Less commonly, the lung may become infected as a consequence of a blood stream infection. Blood-borne pneumonia is seen especially in staphylococcal sepsis (Chapter 296) or right-sided endocarditis (Chapter 76), both of which are more common in intravenous drug users (Chapter 33), and in gram-negative bacteremias, particularly in an immunocompromised host. The lung may also rarely be inoculated directly by penetrating chest trauma or by local spread from a nearby infected organ (bacterial or amoebic liver abscess or paragonimiasis; Chapters 360 and 364) or a contiguous soft tissue infection.

Fortunately, the lung is well equipped to defend against inoculation with most microbes. When large droplets of infected material reach the airways, they are removed by the mucociliary escalator, which sweeps entrapped contents up to the oropharynx, where they are swallowed or expectorated. Smaller particles, in the range of 0.5 to 2.0 μm, are deposited in the alveoli, where alveolar macrophages phagocytize and destroy most pathogens. These macrophages are further activated to release potent cytokines and chemokines, including tumor necrosis factor-α, interleukin-8, and leukotriene B_4, which help recruit neutrophils from the blood stream into the alveolar spaces, where they participate in the uptake and degradation of microorganisms. For many microorganisms such as *S. pneumoniae* (Chapter 297), clearance of infection is greatly facilitated by the development of specific immunoglobulin G that binds the surface of the organisms or their polysaccharide capsule. These specific antibodies, which act as immune opsonins, greatly augment the ability of neutrophils and macrophages to phagocytize and destroy the bacteria. In addition, pattern recognition receptors and other nonimmune opsonins, including surfactant proteins A and D, fibronectin, and vitronectin, also bind to specific epitopes on the surface of organisms that reach the lower respiratory tract and assist in their recognition and elimination. Only when organisms overwhelm or evade these multiple host defense systems does inoculation of the lung result in clinically significant pneumonia.

CLINICAL MANIFESTATIONS

The possibility of pneumonia should be considered in any patient who has new respiratory symptoms, including cough, sputum, or dyspnea, particularly when these symptoms are accompanied by fever or abnormalities on physical examination of the chest, such as rhonchi and rales. The initial manifestation is frequently more subtle in patients who are elderly or have an altered immunologic status; in such patients, nonspecific symptoms, including loss of appetite, confusion, dehydration, worsening of symptoms or signs of other chronic illnesses, or failure to thrive, may be the initial manifestation of pneumonia. Pneumonia is also increasingly prevalent in patients with specific comorbid conditions, including smoking, chronic obstructive pulmonary disease (COPD; Chapter 88), diabetes mellitus, malignancy, heart failure, neurologic diseases, narcotic and alcohol use, and chronic liver disease.

The initial symptoms and signs are often variable from patient to patient and cannot be reliably used to establish a specific (microbiologic) diagnosis. The classic physical findings in lobar pneumonia include evidence of consolidation with altered transmission of breath sounds, egophony, crackles, and changes in tactile fremitus. However, in many patients, the physical findings are subtler and may be limited to scattered rhonchi. A thorough physical examination, posteroanterior and lateral chest radiographs, and a blood leukocyte count with a differential cell count should be performed when pneumonia is suspected. An assessment of gas exchange (oximetry or arterial blood gas determination) should be obtained for all patients who are admitted to the hospital. The clinician needs to be mindful of competing diagnoses that can mimic the findings of pneumonia, such as pulmonary embolism (Chapter 98), bronchogenic and bronchoalveolar carcinoma (Chapter 197), drug-induced lung diseases (Chapter 94), and idiopathic interstitial lung diseases (Chapter 92).

DIAGNOSIS

Even with intensive laboratory investigation, the specific microbiologic cause can be established with certainty only in approximately 50% of patients with pneumonia. The probable predominant organism varies with the host's epidemiologic factors, the severity of illness, and which laboratory approach is used to establish the diagnosis.

Bacterial Pneumonia

S. pneumoniae (Chapter 297) is the organism most frequently detected by culture of sputum or blood. In contrast, *Mycoplasma pneumoniae* (Chapter 325) is frequently detected with serologic tests. Additional bacterial agents include *Haemophilus influenzae* (Chapter 308), *Staphylococcus aureus* (Chapter 296), enteric gram-negative bacilli (Chapters 290 and 314), and *L. pneumophila* (Chapter 322). *Chlamydia* and respiratory viruses have also been implicated in up to 10% of cases. The so-called atypical pathogens,

TABLE 97-1 HOST FACTORS ASSOCIATED WITH SPECIFIC PATHOGENIC CAUSES OF PNEUMONIA

UNDERLYING CONDITION	ASSOCIATED MICROORGANISM
Active smoking/chronic obstructive lung disease	*Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Pseudomonas aeruginosa, Chlamydophila pneumonia*
Nursing home residents	*S. pneumoniae*, gram-negative bacilli, *H. influenzae, Staphylococcus aureus, Chlamydophila pneumonia*, anaerobes, *Mycobacterium tuberculosis*
Alcoholism	*S. pneumoniae* (including drug-resistant strains), gram-negative bacilli, anaerobes, *Mycobacterium tuberculosis, Klebsiella pneumoniae, Acinetobacter species*
Gross aspiration/poor dentition	Anaerobes, gram-negative enteric pathogens
Travel to southwestern United States	*Coccidioides immitis*
Exposure to bats	*Histoplasma capsulatum*
Exposure to birds	*Cryptococcus neoformans, Chlamydia psittaci, H. capsulatum*
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals	*Coxiella burnetii* (Q fever)
Viral influenza	Influenza, *S. aureus, S. pneumoniae, H. influenzae*
Bronchiectasis, cystic fibrosis	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus, Aspergillus* species, *Mycobacterium avium* complex
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Intravenous drug use	*S. aureus*, anaerobes, *M. tuberculosis*, *S. pneumoniae*
Endobronchial obstruction	Anaerobes
Recent antibiotic therapy	Drug-resistant *S. pneumoniae, P. aeruginosa*
HIV (early)	*S. pneumoniae, H. influenza, M. tuberculosis*
HIV (late)	The pathogens listed for early HIV infection, plus *Pneumocystis jirovecii, Cryptococcus, Histoplasma, Aspergillus*, atypical mycobacteria (especially *M. kansasii* and *M. avium* complex), *P. aeruginosa, H. influenza*
In the context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; HIV = human immunodeficiency virus.
Adapted from Infectious Diseases Society of America/American Thoracic Society. Consensus guidelines on the management of community acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:S27-S72.

including *M. pneumoniae, Chlamydia pneumoniae,* and *Legionella* species, are increasingly being recognized as important and prevalent causes of pneumonia. Mixed infections, particularly those related to coinfection with these "atypical" pathogens in addition to the usual bacterial pathogens, have been reported in up to one third of patients with lower respiratory tract infection.

Specific host factors also influence the relative risk for infection with specific microorganisms (Table 97-1). For instance, smokers and those with COPD are at increased risk for invasive *S. pneumoniae,* as well as *H. influenzae, Moraxella catarrhalis* (Chapter 308), and *Legionella* species. Alcoholism is associated with increased risk for drug-resistant *S. pneumoniae,* anaerobic lung infection, and tuberculosis.

The clinician also should solicit information about household and workplace exposure, such as to other ill persons. The clinician should ask about recent travel to specific geographic regions, such as the central United States, where histoplasmosis is endemic (Chapter 340), the Southwest, where coccidioidomycosis is found (Chapter 341), and selected northern and central regions of the United States, where blastomycosis is found (Chapter 342). Recent travel to regions with epidemic viral respiratory infections, including seasonal influenza, avian influenza, H1N1 (swine) influenza, and severe acute respiratory syndrome (SARS), or travel to Asia, Africa, and central and eastern Europe, which are highly endemic for tuberculosis, should be considered (Chapter 332). In addition, environmental exposure, such as to birds (psittacosis), bird droppings (histoplasmosis), bats (histoplasmosis), rabbits (tularemia, Chapter 319), and farm animals (Q fever, Chapter 335), is additional data that should be obtained during the history.

Viral Pneumonia

Although most attention traditionally focuses on bacterial causes of severe community-acquired pneumonia, viruses can also cause serious lower respiratory tract infections. The predominant respiratory viruses that can cause severe pneumonia include various influenza viruses and respiratory syncytial virus (RSV) (Chapter 370). Both influenza virus and RSV can be detected in respiratory secretions, which should be obtained in suspected cases. It is estimated that influenza infections are responsible for in excess of 36,000 respiratory- and circulatory-related deaths annually in the United States, predominantly in elderly patients and those with underlying cardiopulmonary or metabolic disease. Influenza-associated pneumonia should be considered in the differential diagnosis of respiratory infections in high-risk patients with underlying disease and in residents of nursing homes or other chronic care facilities during the season of October through May, especially in patients who have not received appropriate vaccination.

It is also increasingly being appreciated that RSV and parainfluenza (Chapter 371) viruses, although formerly considered mainly infections of pediatric populations, can lead to serious lower respiratory tract infections in adults during the winter season. Host immunity to RSV infection in childhood is incomplete, and recurrent infections can occur in both immune-competent and immune-impaired adults, particularly in elderly patients. It is estimated that RSV is associated with more than 11,000 deaths each year in the United States, with most deaths occurring in elderly people and in patients with chronic cardiopulmonary disease.

Emerging influenza infections must also be considered. Although typical seasonal influenza tends to occur in North America during the months of October to May, novel influenza viruses do not always follow that epidemiology. In particular in the spring and summer of 2009, a novel H1N1 (swine) influenza virus occurred in epidemic proportions in Mexico and rapidly spread over the world. In contrast to many other influenza outbreaks, the virus continued to circulate over the summer months in both the northern and southern hemispheres. H1N1 generally produced a typical syndrome with fever, headaches, cough, malaise, and myalgias. Most cases were mild or self-limited. However, excess hospitalization and mortality from H1N1 infection has been observed in infants, children, and adults younger than 24 years. Pregnant women and children, in particular those who are immunosuppressed, are at particular risk.

Avian influenza A (H5N1; Chapter 372) generally infects wild birds, which carry the H5N1 virus in their intestines, but usually are not made very sick by the virus. However, avian influenza can be highly contagious and fatal among domesticated birds, including chickens, turkeys, and ducks. Transmission to humans has been relatively uncommon, despite the lack of immunity against the virus, but human outbreaks have occurred from contact with infected birds (e.g., domesticated chicken and turkeys) or with secretions or excretions from infected birds.

SARS emerged as an additional form of life-threatening atypical pneumonia that was first detected in the Guangdong Province of China in late 2002, with major outbreaks in Hong Kong, Guangdong, Singapore, and Toronto and Vancouver, Canada. The disease is caused by a novel coronavirus (Chapter 374) with an incubation period of 2 to 10 days. The initial source of the infection remains uncertain, although palm civet cats and Chinese ferret badgers harbor a coronavirus with greater than 99% similarity to human SARS isolates. Worldwide, however, the illness is largely a nosocomial disease, with health care workers representing a significant fraction of the infected individuals. SARS is characterized by an insidious onset of fever, chills, headache, cough, malaise, and dyspnea, with radiologic evidence of pneumonia. Although upper respiratory symptoms are uncommon, voluminous watery diarrhea without mucus or blood develops in up to 70% of patients. SARS is believed to be principally transmitted by respiratory droplets. Current treatment is supportive, with no antiviral agent yet having been proved to be efficacious. SARS pneumonia tends to resolve slowly and spontaneously, usually by the third week of illness. However, the estimated case-fatality rate remains approximately 10%. SARS is highly contagious, and lethal transmission to health care workers has been documented. Isolation procedures and equipment appropriate for SARS include standard, contact, and airborne isolation precautions such as scrupulous hand hygiene, gowning, disposable gloves, the use of N95 respirators, and eye protection. Suspected

cases of SARS require notification of local public health departments and the Centers for Disease Control and Prevention.

Agents of Bioterrorism

Physicians should also be vigilant for clues of pneumonia related to agents of bioterrorism (Chapter 20). These clues can include outbreaks of severe illness and pneumonia in multiple, otherwise healthy individuals or the isolation of unusual organisms in patients with pneumonic illness. The microorganisms most likely to be associated with severe pneumonia during bioterrorism-related inhalation exposure include *B. anthracis* (Chapter 302), *Francisella tularensis* (Chapter 319), and *Y. pestis* (Chapter 320). Inhalational anthrax always indicates a bioterrorism threat, whereas pneumonic plague or tularemia may or may not be associated with bioterrorism.

Radiography

Clinical suspicion of pneumonia should prompt standard posteroanterior and lateral chest radiography. Although the pattern of infiltration can rarely establish a specific microbiologic etiology, chest films are most useful for providing essential information on the distribution and extent of involvement, as well as potential pneumonic complications. Many bacterial pneumonias result in localized alveolar infiltrates and consolidation. Even though pneumococcal pneumonia is classically described as having a lobar distribution, the pattern can be multilobar (Fig. 97-1) or bilateral. The "bulging" fissure sign, which represents lobar filling and consolidation, has traditionally been attributed to *Klebsiella pneumoniae,* but this finding is not specific and can be observed with *S. pneumoniae* and other bacteria and even with bronchoalveolar carcinoma. Diffuse interstitial and alveolar infiltrates should suggest viral infections (cytomegalovirus, influenza virus, or RSV), *L. pneumophila,* or enteric gram-negative pneumonia, particularly in neutropenic patients. These diffuse pulmonary infiltrations can be indistinguishable from other causes of acute respiratory distress syndrome. Diffuse alveolar and interstitial infiltration can also be observed in patients with *Pneumocystis jirovecii* pneumonia (Chapter 349) related to immune suppression, such as in those with acquired immunodeficiency syndrome. Cavitary lesions often indicate a necrotizing infection related to *S. aureus, M. tuberculosis* (Fig. 97-2), and certain endemic fungi such as *Coccidioides immitis, Aspergillus* species infection in an immunocompromised patient (Chapter 347), or anaerobic lung infection with abscess formation. Mediastinal adenopathy and widening have been observed in inhalational anthrax infections.

The chest radiograph provides further important information about potential infectious complications of pneumonia. Pleural effusions (Chapter 99), which occur in a variety of respiratory infections, are best documented with lateral decubitus views or with computed tomography (CT) imaging of the thorax. The discovery of any pleural effusion greater than 10 mm in thickness on a lateral decubitus film or any loculated effusion should prompt thoracentesis to aid in the identification of a complicated parapneumonic effusion or empyema, which may require definitive drainage (Chapter 99). Enlargement of mediastinal and hilar lymph nodes, which is rare in acute bacterial infection, suggests fungal or mycobacterial infection or an underlying lung cancer. Loss of volume of a lung segment or lobe should raise suspicion of postobstructive pneumonia distal to an endobronchial lesion caused by a neoplasm, occult foreign body, or broncholithiasis.

Laboratory Findings

Sputum Gram Stain and Culture

Considerable controversy exists over the appropriate microbiologic evaluation of patients with suspected pneumonia. Despite intensive microbiologic evaluation, a specific organism may not be discovered in half the patients with pneumonia. Furthermore, most patients with pneumonia satisfactorily respond to simple, relatively nontoxic antibiotic regimens based on the most likely organisms causing infection. Thus, the necessity to document the precise cause of the process remains uncertain.

Debate continues over the need to perform a sputum examination with Gram staining in every patient with community-acquired pneumonia. An American Thoracic Society consensus panel has recommended that a sputum Gram stain and culture be obtained primarily if an organism that is resistant to the usual empirical treatment regimens is suspected. To be useful, sputum should contain fewer than 10 squamous cells and more than 25 leukocytes per low-power field; a well-performed Gram stain may reveal a single, predominant organism such as encapsulated gram-positive cocci (pneumococci) or small pleomorphic gram-negative coccobacilli *(Haemophilus).* However, current data have not clearly correlated Gram stain findings with the results of culture of alveolar materials in large numbers of patients with community-acquired pneumonia. Nevertheless, sputum examination can strongly support the diagnosis of certain specific infections, including *M. tuberculosis* (acid-fast stain), endemic fungi (KOH preparations), *P. jirovecii* (methenamine silver or fluorescent antibody stain), or *Legionella* species (direct fluorescent antibody staining). In most cases of community-acquired pneumonia, the general intent of sputum Gram stain examination, if it is performed, should be to detect additional or unusual pathogens and hence to expand rather than narrow the initial antibiotic therapy. All too often, an adequate sputum specimen cannot be obtained, and the Gram stain interpretation may be equivocal. Therefore, the initial therapeutic plan must be based on the most likely pathogens responsible for the pneumonia.

If unusual or drug-resistant pathogens are suspected, sputum specimens should be sent for culture before antibiotic therapy is initiated. When the culture results are available, they should be compared with the predominant organisms observed on Gram stain. Unfortunately, the sensitivity and specificity of sputum culture are not optimal, each being roughly 50%. Antibiotic susceptibility information on an isolated pathogenic organism can, however, be useful both for epidemiologic surveillance and for management of patients who do not respond to initial empirical therapy.

Other Bacterial Cultures

Cultures of normally sterile body fluids such as blood, pleural fluid, or occasionally cerebrospinal fluid (CSF) are highly specific when positive.

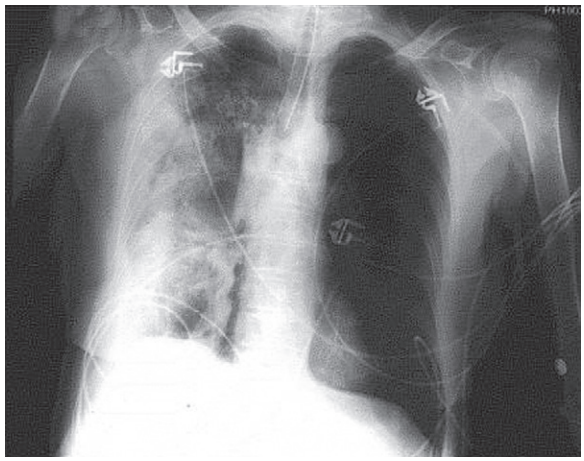

FIGURE 97-1. Radiologic diagnosis of pneumonia. A standard posteroanterior radiograph in a 70-year-old woman demonstrates chronic obstructive pulmonary disease complicated by right multilobar *Streptococcus pneumoniae* pneumonia and empyema.

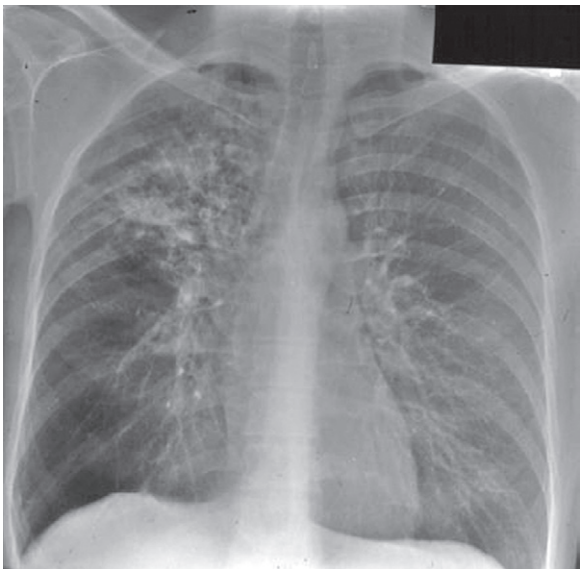

FIGURE 97-2. Cavitary lesions. A posteroanterior radiograph in a 54-year-old man with cough and fever shows a right upper lobe cavitary process caused by *Mycobacterium tuberculosis* infection.

Approximately one fourth of patients with bacterial pneumonia have demonstrable bacteremia. Blood should be drawn for culture before administration of antibiotics in patients with serious illness attributable to pneumonia, and diagnostic thoracentesis should be performed if an effusion is large enough to be aspirated safely. CSF examination is generally reserved for patients with additional signs and symptoms of meningeal irritation (Chapter 420) or abnormalities on neurologic examination.

Testing for Suspected Bioterrorism

Recommended testing for suspected anthrax includes blood culture and chest CT scanning. For the diagnosis of pneumonic plague, blood culture as well as sputum Gram stain and culture are advised. For tularemic pneumonia, cultures should be obtained from blood, sputum, and the pharynx. Culture of these extremely virulent organisms should be undertaken in a level 3 (BL3) biocontainment laboratory.

Immunologic Studies

Immunologic techniques such as immunofluorescence, enzyme-linked immunosorbent assay, antigen detection, polymerase chain reaction, and DNA hybridization may be considered when specific organisms are strongly suspected on clinical grounds, but these tests are not routinely indicated in most cases of community-acquired pneumonia. For example, *Legionella* urinary antigen screening and acute and convalescent serologic evaluation may be helpful when *L. pneumophila* pneumonia is suspected (Chapter 322). *Legionella* urinary antigen testing may underdiagnose infections caused by organisms other than *Legionella* serogroup 1. Furthermore, the judicious use of fungal serology can detect endemic mycoses, particularly histoplasmosis and coccidioidomycosis (Chapters 340, 341, and 342). Histoplasmosis can also be confirmed by urinary antigen testing with high sensitivity. The measurement of *Aspergillus galactomannan* antigen in serum can be a useful adjunct in the diagnosis of invasive *Aspergillus* pneumonia in various immunocompromised patients. Bronchoscopy with lavage for immunostaining may, in selected circumstances, provide enhanced sensitivity, such as in the diagnosis of *P. jirovecii* pneumonia (Chapter 349).

Viral Studies

Rapid antigen detection tests are now available, with tests that distinguish between influenza A and B being preferred. These tests are currently recommended for epidemiologic purposes in the community and also help direct individual therapy. RSV antigen detection tests are likewise available, but they are relatively less sensitive when applied to sputum in adult patients. A variety of other assays, including polymerase chain reaction (PCR) and specialized antigen testing, are available in reference laboratories for detection of diagnosis of novel H1N1 (swine) influenza, H5N1 (avian) influenza, and the SARS coronavirus.

Bronchoscopy

Invasive sampling of respiratory secretions is not usually necessary in patients with community-acquired pneumonia. Flexible fiberoptic bronchoscopy with a protected catheter brush and bronchoalveolar lavage (BAL) sampling has largely supplanted transtracheal and transthoracic needle aspiration. Bronchoscopy is indicated in selected clinical situations in which a delay in accurate diagnosis may have serious consequences, such as in immunocompromised hosts or patients whose condition has worsened despite initial antimicrobial therapy. Other indications for bronchoscopy in the setting of apparent community-acquired pneumonia include either lung abscess detected on a chest radiograph (Chapter 84) or evidence of volume loss and distal consolidation suggesting endobronchial obstruction.

PREVENTION

In light of the significant morbidity and potential mortality of pneumonia, appropriate measures should be instituted to reduce the possibility of lung infection. Important but often neglected interventions include smoking cessation (Chapter 31) and avoidance of illicit drugs (Chapter 33) or excess alcohol (Chapter 32), which may impair consciousness. Optimizing the patient's nutritional status is also important in that markedly underweight or obese patients are at increased risk. Finally, the appropriate and consistent use of vaccines can strongly reduce the risk for pneumonia in appropriate patient populations (Chapter 17). The current pneumococcal vaccine contains 23 purified capsular polysaccharides from the serotypes of *S. pneumoniae* that are responsible for more than 85% of invasive pneumococcal infections. Overall, this vaccine is approximately 50 to 80% effective in preventing death from invasive infection. Accordingly, current recommendations are that it should be administered to all patients older than 65 years and to patients younger than 65 years who have chronic pulmonary disease, heart disease, diabetes mellitus, alcoholism, chronic liver disease, CSF leaks, or asplenia and to patients who live in certain settings, including Alaskan natives, high-risk Native American populations, and patients in long-term care facilities. Current pneumococcal vaccines have little toxicity, limited mainly to local site irritation. Individuals generally receive one dose of vaccine, but a single revaccination 5 years later should be considered in those who received their vaccination before 65 years of age or who are at increased risk for severe pneumonia. Pneumococcal vaccine can safely be administered at the time of hospitalization for community-acquired pneumonia.

Vaccination (Chapter 17) should also be considered for viral influenza (Chapter 372). Although usually manifested as an upper respiratory tract infection, influenza can itself cause pneumonia in both immunocompetent and immunosuppressed individuals. More commonly, influenza may precipitate a subsequent bacterial infection, often with *S. aureus, H. influenzae,* and *S. pneumoniae*. Influenza vaccines are developed annually against the current influenza strains, so annual revaccination is necessary (Chapter 17). Influenza vaccines are estimated to be roughly 80% effective in preventing mortality related to influenza. The vaccine should be considered in all patients older than 50 years; residents of nursing homes and chronic care facilities; persons with chronic pulmonary, cardiac, or other diseases requiring ongoing medical care; pregnant women in the second or third trimester during influenza season; and all health care workers with direct patient contact. A weakened virus vaccine, which is administered through a nasal application, does not cause influenza and is approved for healthy people 2 years to 49 years of age who are not pregnant. An inactivated vaccine containing killed virus, administered by injection, is approved for people 6 months of age and older, including healthy people, people with chronic medical conditions, and pregnant women. Both have demonstrated efficacy in preventing influenza and its related complications, including pneumonia.

Contraindications to influenza vaccine include allergy to raw eggs or thimerosal. Side effects are generally self-limited and include injection site soreness, myalgias, mild fever, and malaise. Seasonal influenza vaccination does not lead to exacerbations of asthma. The vaccine should be administered in the fall of the year, but it can also be administered during local epidemics.

TREATMENT Rx

Oversight agencies are increasingly focused on objective measures of optimal care for community-acquired pneumonia, particularly in the hospital setting. Although recommendations are evolving and sometimes vary, current recommendations are that hospitalized patients with community-acquired pneumonia should undergo assessment of oxygenation, initiation of antibiotic therapy in the emergency department, drawing of blood for culture before antimicrobial initiation, smoking cessation intervention, and review and update of immunization status. Most experts also advise chest radiography at the time of admission. The use of biomarkers for bacterial infection, such as levels of procalcitonin, may prove to be helpful when determining which patients can avoid immediate antibiotics or discontinue initial empirical antibiotics because of a low likelihood of bacterial infection.

Initial Empirical Therapy

Because the microbiologic etiology of community-acquired pneumonia is determined in only approximately 50% of cases and the diagnosis may take a day or two, the clinician must institute appropriate empirical therapy based on the most likely agents contributing to the lung infection (Table 97-2). When possible, empirical therapy should be initiated as soon as possible after the diagnosis is established—immediately in the outpatient setting and in the emergency department if the patient is hospitalized. Empirical antimicrobial therapy is based on the severity of illness (inpatient or outpatient setting) and should broadly cover the most likely organisms. The most common bacterial pathogens are *S. pneumoniae* (Chapter 297) and *H. influenzae* (Chapter 308); however, the so-called atypical pathogens, including *M. pneumoniae, C. pneumoniae,* and *Legionella* species (Chapters 325, 326, and 322, respectively), can be the primary or coinfecting agents in up to 40% of community-acquired pneumonia and must be covered in empirical antibiotic regimens. Therapy can be narrowed later after any relevant culture information is obtained.

Guidelines for Hospital and Intensive Care Unit Admission and Treatment

Under current guidelines, patients are stratified with respect to where treatment is initiated (outpatient, inpatient, or ICU setting), the presence of underlying cardiopulmonary disease, and other modifying factors, such as whether

TABLE 97-2 MOST COMMON MICROBIOLOGIC CAUSES OF COMMUNITY-ACQUIRED PNEUMONIA IN APPROXIMATE ORDER OF FREQUENCY

OUTPATIENTS	HOSPITALIZED PATIENTS	SEVERE PNEUMONIA/ICU
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*Staphylococcus aureus*
Haemophilus influenzae	*C. pneumoniae*	*Legionella* species
Chlamydophila pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses	*Legionella* species Aspiration Respiratory viruses	*H. influenzae*

Adapted from Infectious Diseases Society of America/American Thoracic Society. Consensus guidelines on the management of community acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:S27-S72.

TABLE 97-3 TRIAGE GUIDELINES FOR COMMUNITY-ACQUIRED PNEUMONIA

DECISION TO ADMIT TO THE HOSPITAL

Follow CURB-65 Guidelines and admit patients who have two or more of the following:
- Confusion
- Uremia (with blood urea nitrogen ≥20 mg/dL)
- Respiratory rate >30 breaths/min
- Blood pressure ≤90 mm Hg systolic or <60 mm Hg diastolic
- Age ≥65 yr

INDICATIONS FOR ICU ADMISSION (1 MAJOR AND ≥3 MINOR)

Major Criteria

Hypotension requiring vasopressors
Respiratory compromise requiring mechanical ventilation

Minor Criteria

Respiratory rate >30 breaths/min
PaO_2/FIO_2 ratio ≤250
Multilobar infiltrate
Confusion/disorientation
Uremia (blood urea nitrogen ≥20 mg/dL)
Leukopenia (white blood cell count ≤4000 cells/mm^3)
Thrombocytopenia (platelets ≤100,000 cells/mm^3)
Hypothermia (≤36° C)
Hypotension requiring aggressive fluid resuscitation

TABLE 97-4 EMPIRICAL TREATMENT GUIDELINES FOR COMMUNITY-ACQUIRED PNEUMONIA

OUTPATIENT MANAGEMENT

1. Previously healthy patients without comorbidities and no use of antimicrobials within the prior 3 months
   A macrolide (preferred) (e.g., clarithromycin, extended release, 1000 mg orally each day for at least 5 days, or azithromycin, 500 mg orally on day 1, followed by 250 mg orally each day on days 2-5)
   Doxycycline, 100 mg orally twice daily for at least 5 days
2. Presence of comorbidities such as chronic cardiopulmonary, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or drugs; or use of antimicrobials in the prior 3 months (if so, select an alternative agent from a different class)
   A respiratory fluoroquinolone (oral moxifloxacin, 400 mg/day, or gemifloxacin, 320 mg/day, or levofloxacin, 750 mg daily for at least 5 days), *or*
   A β-lactam (e.g., ceftriaxone, 1-2 g IM each day for at least 5 days) *plus* a macrolide (e.g., azithromycin, 500 mg orally on day 1, followed by 250 mg orally each day on days 2-5)
3. In regions with a high rate (>25%) of infection with high-level (MIC ≥16 mg/mL) macrolide-resistant *Streptococcus pneumoniae*, consider an alternative agent as noted under (2) for patients without comorbidities.

INPATIENTS, NON-ICU MANAGEMENT

1. A respiratory fluoroquinolone (moxifloxacin, 400 mg/day, or gemifloxacin, 320 mg/day, or levofloxacin, 750 mg IV for 2 days followed by oral for at least 5 days total), *or*
2. A β-lactam (e.g., ceftriaxone 1-2 g IV daily for at least 1-2 days, followed by 1-2 g IM daily for at least 5 days total), *plus*
   A macrolide (azithromycin, 500 mg IV each day for at least 2 days, followed by 500 mg orally each day for a total of at least 5 days)

INPATIENTS—ICU MANAGEMENT

1. A β-lactam (cefotaxime, 1-2 g IV every 6-8 hr, or ceftriaxone, 1-2 g IV each day, or ampicillin-sulbactam, 1.5-3 g IV every 6 hours, up to maximum of 4 g of sulbactam/day, for 7-14 days, *plus*
   Either azithromycin, 500 mg IV each day for at least 2 days, followed by 500 mg orally each day for a total of at least 5 days, or a respiratory fluoroquinolone (e.g., moxifloxacin, 400 mg/day, or gemifloxacin, 320 mg/day, or levofloxacin, 750 mg IV daily for 7-14 days)
2. For penicillin-allergic individuals, a respiratory fluoroquinolone (e.g., moxifloxacin, 400 mg/day, or gemifloxacin, 320 mg/day, or levofloxacin, 750 mg IV daily for 7-14 days) and aztreonam, 2 g IV every 6-8 hr for 7-14 days, are recommended.

SPECIAL CONCERNS

If *Pseudomonas* species infection is a concern:
1. An antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, 3.375 g IV every 6 hr, or cefepime, 1-2 g every 12 hr, or imipenem, 500 mg every 6 hr or 1 g every 8 hr, or meropenem, 1 g IV every 8 hr), *plus* either ciprofloxacin, 400 mg IV every 8 hr, or levofloxacin, 500-750 mg IV every day, for 7-14 days, *or*
2. The above β-lactam plus an aminoglycoside (e.g., gentamicin, 7 mg/kg/day in three divided doses, with monitoring to maintain trough levels lower than 1 μg/mL, or tobramycin, 7 mg/kg/day in three divided doses, with monitoring to maintain trough levels lower than 1 μg/mL) and azithromycin (500 mg IV each day for at least 2 days, followed by 500 mg orally each day) for 7-14 days, *or*
3. The above β-lactam plus an aminoglycoside (as described above) and an antipneumococcal fluoroquinolone (ciprofloxacin, 400 mg IV every 8 hr, or levofloxacin, 500-750 mg IV every day) for 7-14 days

For penicillin-allergic patients, use aztreonam, 2 g IV every 6-8 hr for 7-14 days, instead of the β-lactam.
If community-acquired methicillin-resistant *Staphylococcus aureus* is a consideration, add vancomycin, 15 mg/kg every 12 hr with monitoring to maintain trough at 15-20 μg/mL, or linezolid, 600 mg every 12 hr, for 7-14 days.

Adapted from Infectious Diseases Society of America/American Thoracic Society. Consensus guidelines on the management of community acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:S27-S72.

the patient is likely to be infected with drug-resistant *S. pneumoniae,* gram-negative enteric bacilli, or *Pseudomonas aeruginosa.* Following these guidelines reduces the number of hospital admissions without adversely affecting outcomes.

The decision to admit a patient to the hospital must be made on clinical grounds. Patients can be effectively and safely managed as outpatients if they are mildly ill, are younger than 65 years, and do not have coexisting cardiopulmonary disease, malignancy, immune compromise, or renal, liver, or other significant systemic diseases (Table 97-3).

In general, outpatients who are mildly ill and do not have any underlying cardiopulmonary disease or other modifying factors are usually infected with *S. pneumoniae, M. pneumoniae, C. pneumoniae, H. influenzae,* respiratory viruses, or *Legionella* species. These uncomplicated outpatient cases can be managed with an oral advanced-generation macrolide, such as azithromycin or clarithromycin, both of which are better tolerated and provide better coverage of *Haemophilus* species than erythromycin.[2] Alternatively, doxycycline may be used in patients who are intolerant of macrolides, although this option is less optimal because of increasing levels of tetracycline resistance in *S. pneumoniae* isolates. Outpatients who have underlying comorbidities (e.g., chronic heart, lung, liver, or renal disease, diabetes mellitus, alcoholism, asplenia, immunosuppressive conditions or drugs, use of antibiotics within the past 3 months, or exposure to a child in a daycare center) are at higher risk of having drug-resistant *S. pneumoniae*. If their pneumonia is not sufficiently severe to warrant admission, and any comorbid illnesses are stable and compensated, patients can be treated either with respiratory fluoroquinolones (e.g., moxifloxacin, gemifloxacin, or levofloxacin) or with a β-lactam plus a macrolide (e.g., high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide) (Table 97-4). In regions that have a high incidence of macrolide-resistant (>25%) *S. pneumoniae,* the alternative agents should be used. When pneumonia is treated on an outpatient basis, patients require careful monitoring to be certain that they respond over the first 72 hours of therapy. The clinician must maintain vigilance about the need to hospitalize patients who deteriorate or fail to respond to the initial empirical therapy.

Patients who have more severe respiratory illnesses, significant unstable or uncompensated comorbid illnesses, or a poor initial response to otherwise

appropriate outpatient therapy generally should be admitted to the hospital promptly. Patients who require hospitalization but not intensive care should be treated initially with either an intravenous respiratory fluoroquinolone, such as levofloxacin or moxifloxacin, or with the combination of an intravenous β-lactam plus a macrolide.

Patients who have respiratory insufficiency, septicemia, shock, or significant multiorgan dysfunction, with or without the need for mechanical ventilatory support, require management in an ICU and evaluation to exclude infection with *P. aeruginosa* (Chapter 314). ICU admission should also be considered for patients who exhibit three or more of the minor criteria for severe community-acquired pneumonia (see Table 97-3).

Among patients with severe community-acquired pneumonia, those at increased risk for *P. aeruginosa* infection include patients with structural lung disease (particularly bronchiectasis), greater than 10 mg/day of previous corticosteroid therapy, neutropenia, malnutrition, or previous broad-spectrum antibiotics for more than 7 days in the past month. ICU patients who are *not* considered at risk for *P. aeruginosa* infection can be treated initially with a β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a respiratory fluoroquinolone (moxifloxacin or levofloxacin) (see Table 97-4). In penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam is a reasonable regimen. Fluoroquinolone monotherapy is not considered appropriate in the setting of severe community-acquired pneumonia. In the ICU population considered to be at risk for *P. aeruginosa* infection, combination antipseudomonal therapy should be used, including an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin or a β-lactam plus an aminoglycoside and azithromycin. If community-acquired methicillin-resistant *S. aureus* (MRSA) infection is a consideration, vancomycin or linezolid should be added to the regimen.

Suspected or Proven Viral Infection

Therapies for suspected and proven viral infection are relatively limited when compared with those for bacterial infections. Early treatment of influenza A or B within the first 48 hours of symptoms with oseltamivir (75 mg orally taken twice daily for 5 days), or zanamivir (two inhalations of 5 mg per inhalation every 12 hours for 5 days) is effective in reducing symptoms and the duration of illness (Chapter 368). Both agents have been used for novel H1N1 swine influenza, and oseltamivir may also have activity against H5N1 bird flu. Empirical antibiotic treatment of possible bacterial superinfection in addition to influenza should include agents effective against *S. pneumoniae* (Chapter 297), *S. aureus* (Chapter 296), and *H. influenzae* (Chapter 308). In these considerations, amoxicillin-clavulanate, cefpodoxime, cefprozil, cefuroxime, or a respiratory fluoroquinolone would be appropriate. Pneumonias caused by varicella-zoster and herpes simplex virus should be treated with parenteral acyclovir (10 mg/kg intravenously every 8 hours for 7 days) (Chapters 382 and 383). No antiviral agents have established efficacy against RSV in adults, parainfluenza virus, adenovirus, metapneumovirus, the SARS coronavirus, or hantavirus. Treatment is largely supportive, with oxygen and ventilator therapy as necessary.

Duration of Therapy

Most patients respond to empirical antibiotic regimens over the first 3 days of therapy. In general, it is not advisable to alter the antibiotic program in the first 72 hours unless the patient is deteriorating or culture results indicate alternative therapy. Patients initially begun on parenteral therapy may be switched to an oral regimen when they are afebrile (temperature less than 38° C [100° F] on two occasions 8 hours apart) and demonstrate improvement in cough, dyspnea, and leukocytosis.

Patients with community-acquired pneumonia should be treated for at least 5 days, should be afebrile for at least 48 to 72 hours, and should not show signs of clinical instability before discontinuation of antibiotic therapy. Accordingly, the total duration of antimicrobials should be individualized to the patient's clinical response. Initial multiagent regimens of a β-lactam with the addition of macrolides for the coverage of *Legionella* and *Mycoplasma* can frequently be de-escalated after several days to the β-lactams alone if *Legionella* urinary antigen and *Mycoplasma* serology prove negative. The clinical caveat remains, however, that macrolides may still be required in clinical situations in which a strong clinical suspicion for *Legionella* persists because urinary antigen testing does not detect organisms other than *Legionella* serogroup 1. Furthermore, in situations in which a causative organism is isolated from a normally sterile site, such as blood or pleural fluid, antibiotic therapy should be simplified and directed by susceptibility testing. Finally, when alternative clinical diagnoses other than pneumonia are proved to be the cause of the respiratory symptoms and all cultures remain negative over the first 72 hours, antibiotic therapy may be safely discontinued.

Treatment Failure

Treatment failures occur in approximately 10% of patients with community-acquired pneumonia, and complications occur in roughly 25% of patients. Adherence to treatment guidelines, such as those described earlier, increases the likelihood of a good outcome.

For patients who do not respond to initial empirical coverage, an aggressive search should be undertaken to detect unusual pathogens, alternative diagnoses such as pulmonary embolism (Chapter 98), or complications of pneumonia such as a complicated pleural effusion (Chapter 99), empyema, or lung abscess (Chapter 90). Additional diagnostic testing may include a chest CT scan, sampling of pleural fluid, and bronchoscopy with collection of respiratory secretions, brushings, and BAL fluid for microbiologic analysis.

Follow-Up after Treatment

Even when the patient appears to respond to the initial antibiotic regimen, the chest radiograph signs resolve more slowly (over a period of 6 to 8 weeks) than other clinical signs and symptoms. The physician must document that abnormalities on the chest radiograph have resolved completely or, in some cases, have led to the formation of a fibrotic scar. Usual practice includes performing repeat radiography 6 to 8 weeks after completion of the antibiotic regimen. Persistence of abnormalities on the chest radiograph or the development of recurrent pneumonia in a similar distribution should prompt a careful search for an underlying endobronchial obstruction such as an occult neoplasm (Chapter 197), foreign body, bronchostenosis, or broncholithiasis. Follow-up CT scanning is usually the prelude to formal pulmonary consultation for consideration of bronchoscopy and other further diagnostic tests.

ASPIRATION PNEUMONIA

EPIDEMIOLOGY AND PATHOBIOLOGY

Although microaspiration is the mechanism underlying most cases of pneumonia, the clinician is occasionally confronted with recurrent bacterial pneumonia in a patient experiencing repeated gross aspiration of oropharyngeal contents. Most of these patients have difficulty swallowing related to either underlying neuromuscular disorders or altered sensorium as a result of medications, drugs or alcohol, or underlying neurologic diseases. Common clinical scenarios associated with recurrent aspiration pneumonia include tracheobronchial fistulas secondary to esophageal or tracheal malignancies, esophageal obstruction related to esophageal cancer and its treatment (Chapter 198), and a wide variety of neurologic disorders, including amyotrophic lateral sclerosis (Chapter 418), multiple sclerosis (Chapter 419), stroke (Chapter 414), and other myopathic processes. Other patients with severe esophageal reflux (Chapter 140) may also experience significant aspiration during sleep despite apparently normal deglutition mechanisms and protective reflexes during wakefulness. Patients with neuromuscular disorders tend to have greater difficulty swallowing thin or liquid materials, whereas patients with obstruction from either malignancy or benign strictures tend to have the greatest difficulty swallowing solid food.

CLINICAL MANIFESTATIONS

Aspiration pneumonias tend to have a less acute manifestation than the usual bacterial pneumonias, with the onset of fever, dyspnea, purulent sputum, malaise, and other systemic symptoms, including loss of appetite, evolving over a number of days. Physical examination of the chest generally reveals only coarse rhonchi in the lower lobes or dependent lung regions.

DIAGNOSIS

The diagnosis of aspiration pneumonia relies foremost on maintaining a high clinical index of suspicion. Recovery of tracheal secretions containing food particles or lipid-laden macrophages strongly supports the diagnosis. In patients receiving tube feedings, the respiratory secretions should be tested for glucose because these secretions normally contain low levels of glucose. Alternatively, methylene blue or similar tracer dyes can be added to tube feeding materials to confirm the presence of aspiration. Additional diagnostic modalities include the use of cineradiographic swallowing studies with thin liquid water-soluble contrast agents to confirm the aspiration event. Radionuclide imaging studies may also document aspiration in adults whose neurologic status precludes them from cooperating fully with the cineradiographic studies. Overnight esophageal pH monitoring may be undertaken in individuals who are suspected of having recurrent esophageal reflux and aspiration events at night. However, except in the most severe cases, it remains difficult to predict which patients with gastroesophageal reflux will actually experience aspiration pneumonia.

Chest radiographs should be reviewed in light of the patient's probable position during aspiration. The lower lobes, particularly the superior segments of the right lower lobe, and the posterior segments of the upper lobes are frequently involved. However, unilateral aspiration or aspiration into

virtually any pulmonary segment has been reported, depending on the patient's position during the aspiration event. The radiographic appearance usually reflects a parenchymal bronchopneumonia process. Pleural involvement is uncommon initially, unless aggressive anaerobic infection is present. Nonresolving or inadequately treated aspiration pneumonia can result in lung abscess and empyema formation.

Bronchoscopy, although not routinely necessary, can confirm the presence of aspiration by recovering food particles or lipid-laden macrophages derived from fats present in the aspirated food. Bronchoscopy with BAL can be useful in providing quantitative counts of aerobic bacteria, and protected specimen brush sampling can document anaerobic organisms, although negative cultures do not exclude the presence of anaerobes.

Microbiology

Oropharyngeal secretions contain massive numbers of microorganisms, with counts of aerobic bacteria ranging between 10^6 and 10^8 and anaerobic organisms being as high as 10^9 per milliliter of saliva. Accordingly, aspiration pneumonia should be viewed as a polymicrobial infection, with the clinical manifestations being driven by the predominant and most aggressive organisms in the mixture. Oropharyngeal colonization is strongly influenced by the clinical setting in which the patient was dwelling at the time of aspiration (outpatient versus hospital or institutional). In otherwise healthy outpatients, aggressive organisms such as *S. pneumoniae, S. aureus,* and *H. influenzae* may also be present. In contrast, the oropharyngeal secretions of hospitalized patients and residents of long-term care facilities include aerobic gram-negative bacteria and *P. aeruginosa.* Anaerobic organisms, which are a major consideration in both settings, include anaerobic and microaerophilic streptococci, *Bacteroides* species, *Fusobacterium nucleatum,* and *Prevotella* species. Cultures of sputum and tracheal secretions probably document such mixed flora.

TREATMENT

Rx

Empirical antibiotic therapy should be initiated rapidly once the diagnosis of aspiration pneumonia is made; the regimen can be modified later after culture information from sputum, tracheal secretions, or bronchoscopic sampling is available. Otherwise healthy individuals with isolated aspiration pneumonia related to trauma, seizures, or oversedation may be treated initially with either oral amoxicillin-clavulanate (amoxicillin, 875 mg, and clavulanate acid, 125 mg, orally every 12 hours for at least 5 days), intravenous clindamycin (600 mg intravenously [IV] every 8 hours for at least 5 days), or intravenous piperacillin-tazobactam (3.375 g IV every 6 hours for at least 5 days), depending on the severity of illness. In uncomplicated mild to moderate aspiration pneumonia in elderly patients, intravenous clindamycin is as effective, less expensive, and associated with a lower rate of post-treatment occurrence of MRSA.[5] For patients with underlying chronic diseases, intravenous piperacillin-tazobactam (3.375 g IV every 6 hours for 7 to 14 days) or intravenous fluoroquinolones that cover anaerobes, such as moxifloxacin (400 mg IV each day for 7 to 14 days), can be considered. In seriously ill individuals, particularly patients requiring intubation and mechanical ventilation, as well as patients experiencing aspiration in the hospital or long-term care setting, coverage must be extended to aerobic gram-negative bacteria and *Pseudomonas* species; treatment considerations would include extended-spectrum β-lactam/β-lactamase inhibitor combinations such as piperacillin-tazobactam (3.375 g IV every 6 hours for 7 to 14 days) or ticarcillin-clavulanate (3 g of ticarcillin, and 0.1 g of clavulanic acid IV every 4 to 6 hours for 7 to 14 days), or carbapenems such as imipenem (500 mg IV every 6 to 8 hours for 7 to 14 days). Intravenous clindamycin (600 mg IV every 8 hours) can also be added in these settings, or alternatively, intravenous clindamycin can be given in combination with ciprofloxacin (400 mg IV every 8 hours for 7 to 14 days) or aztreonam (2 g IV every 6 to 8 hours for 7 to 14 days). In patients with concern about organisms with high levels of antibiotic resistance, such as *P. aeruginosa,* an antipseudomonal β-lactam such as ceftazidime (2 g IV every 8 hours for 7 to 14 days) or cefepime (1 to 2 g every 12 hours for 7 to 14 days) can be combined with an antipseudomonal fluoroquinolone such as ciprofloxacin or an aminoglycoside (e.g., gentamicin 7 mg/kg/day in three divided doses IV for 7 to 14 days, measuring drug levels and adjusting doses to achieve a trough level of <1 µg/mL). Again, addition of extended anaerobic coverage with clindamycin should be considered. Finally, if the patient is known or suspected to harbor MRSA, intravenous vancomycin (15 mg/kg every 12 hours IV and measuring drug level and adjusting doses to achieve trough levels of 15 to 20 µg/mL) or linezolid (600 mg IV every 12 hours) for 10 to 14 days should be added to the regimen.

Surgical Therapy

Adequate nutrition is a concern in patients with multiple episodes of aspiration pneumonia and underlying neurologic disease or malignancy. Endoscopic or surgical placement of a gastrostomy or jejunostomy feeding tube can be considered to aid in providing nutrition, fluids, and medications in the palliation of such patients. Of greater challenge are patients who continue to have pneumonia related to aspiration of saliva, sometimes around cuffed endotracheal and tracheostomy tubes. If aggressive therapy is considered appropriate, ligation of the submaxillary and parotid salivary ducts can decrease the production of saliva.

HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTH CARE–ASSOCIATED PNEUMONIA

EPIDEMIOLOGY

Hospital-acquired pneumonia, ventilator-associated pneumonia, and health care–associated pneumonia represent the second most common nosocomial infections in the United States. Hospital-acquired pneumonia on average increases the length of hospital stay from 7 to 9 days, at an additional cost of more than $40,000 per patient; it is responsible for one fourth of all ICU infections and half of all antibiotic use. Early-onset hospital-acquired pneumonia and ventilator-associated pneumonia, defined as infections occurring within the first 4 hospital days, tend to be caused by antibiotic-susceptible bacteria, whereas late-onset infections are more frequently caused by multidrug-resistant (MDR) organisms (Table 97-5), which are associated with greater morbidity and mortality. The overall mortality attributed to hospital-acquired pneumonia may be as high as 30 to 50%.

PATHOBIOLOGY

Gram-negative bacterial pneumonias are fairly uncommon in previously healthy outpatients, except in patients with impaired immunity or underlying structural lung disease such as chronic obstructive pulmonary disease. However, aerobic gram-negative bacilli, including *P. aeruginosa, Escherichia coli, K. pneumoniae,* and *Acinetobacter* species, play major roles in patients with hospital-acquired pneumonia, ventilator-associated pneumonia, and health care–associated pneumonia. Many cases are polymicrobial, and gram-positive agents such as *S. aureus,* particularly MRSA strains, are also increasingly common. The frequency of MDR bacteria varies by the patient population, hospital, ICU, and local use of antimicrobial agents, so routine surveillance and monitoring of local pathogens and drug susceptibilities are key to adjusting antibiotic use appropriately.

P. aeruginosa, Acinetobacter species, *Stenotrophomonas maltophilia,* and *Burkholderia cepacia* complex are of particular concern because these organisms rapidly become resistant to multiple classes of antibiotics. MDR organisms are most commonly found in patients with severe underlying chronic disease, in patients with health care–associated pneumonia, and in those with late-onset hospital-acquired pneumonia and ventilator-associated pneumonia. Although considerable emphasis is placed on gram-negative bacteria in the hospital setting, more traditional bacterial pathogens such as *S. pneumoniae* and *H. influenzae* must also be considered as potential causes.

TABLE 97-5 HOST RISK FACTORS ASSOCIATED WITH DEVELOPMENT OF MULTIDRUG-RESISTANT INFECTION DURING HAP, VAP, AND HCAP

Antibiotic therapy in the past 90 days
High incidence of antibiotic resistance in the community or in the specific hospital unit
Current hospitalization for 5 or more days
Immunosuppressive disease or therapy
Presence of risk factors for HCAP
Hospitalization for 2 or more days in the past 90 days
Resident in a nursing home or extended care facility
Home infusion therapy (including antibiotics)
Chronic dialysis within the past 30 days
Home wound care
Family member with an MDR pathogen

HAP = hospital-associated pneumonia; HCAP = health care-associated pneumonia; MDR = multidrug resistant; VAP = ventilator-associated pneumonia.
Adapted from American Thoracic Society and Infectious Diseases Society of America. Guidelines for management of adults with hospital-acquired, ventilator-associated, and health care-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388-416.

L. pneumophila also occasionally occurs as a nosocomial infection, particularly where there is contaminated water or during construction.

CLINICAL MANIFESTATIONS

Hospital-acquired pneumonia, ventilator-associated pneumonia, and health care–associated pneumonia are often first suspected with the demonstration of new or worsening radiographic infiltrates along with other clinical signs of infection, including fever, leukocytosis, and purulent sputum. Oxygenation may have also worsened. In general, two of the three major clinical features (fever, leukocytosis, purulent sputum) should be present. In patients with acute respiratory distress syndrome, however, a single clinical factor alone should prompt additional investigation and microbiologic culture.

DIAGNOSIS

All patients with suspected hospital-acquired pneumonia, ventilator-associated pneumonia, and health care–associated pneumonia should receive a comprehensive history and physical examination to define the severity of disease and potential sources of infection. Chest radiography is essential to determine the extent of pneumonia, particularly whether it is focal or multilobar. Some patients without new or evolving radiographic infiltrates but with other signs of infection may have purulent tracheobronchitis (Chapter 96), which may require antibiotic therapy if clinical signs of infection are present. Arterial blood gases, complete blood count, electrolytes, and liver and renal function should also be evaluated. Blood should be obtained for culture, although it is positive in only a minority of patients, before instituting new antibiotics whenever possible.

Lower respiratory tract secretions should be obtained for culture from all patients by endotracheal aspiration, BAL, or protected specimen brush whenever possible before changes in antibiotic therapy; a reliable Gram stain can help direct initial empirical therapy. A sterile culture of lower respiratory tract secretions in the absence of a new antibiotic in the past 72 hours essentially excludes most bacterial pneumonias with a 94% negative predictive value, although *Legionella* and viral infection are still possible in this situation. The quantitative diagnostic threshold for significant bacterial infection, in the absence of recent (<72 hours) changes in antibiotic regimens, is as follows: greater than 10^6 colony-forming units (cfu)/mL for tracheal aspirates, greater than 10^4 or 10^5 cfu/mL for quantitative BAL fluid, and greater than 10^3 cfu/mL for protected specimen brushings. The use of bronchoscopically obtained specimens and quantitative bacterial culture in directing therapy reduces the 14-day mortality in suspected ventilator-associated pneumonia.

TREATMENT

Initial Empirical Therapy

If the patient is unstable or has evidence of sepsis, or if there is a high suspicion for hospital-acquired pneumonia, ventilator-associated pneumonia, or health care–associated pneumonia, prompt antibiotic therapy is required regardless of whether bacteria are found on the initial microscopic examination of lower respiratory tract samples because delays in antimicrobial therapy increase mortality. The choice of initial empirical therapy is based on several factors, including whether the pneumonia is early onset, whether there are risk factors for MDR bacterial infections (Table 97-6), and local surveillance data on bacterial prevalence and susceptibilities.

Suspected or Early-Onset Disease

For patients with suspected hospital-acquired or ventilator-associated pneumonia, with early-onset disease, and with no identifiable risk factors for MDR organisms, initial empirical therapy can include either ceftriaxone, an intravenous fluoroquinolone (levofloxacin, moxifloxacin, or ciprofloxacin), ampicillin/sulbactam, or ertapenem. These options will cover *S. pneumoniae,*

TABLE 97-6 EMPIRICAL ANTIBIOTIC TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTH CARE–ASSOCIATED PNEUMONIA

GROUP A: PATIENTS WITH EITHER HAP OR VAP, WITHOUT RISK FACTORS FOR MDR PATHOGENS, AND WITH EARLY-ONSET PNEUMONIA	
POTENTIAL PATHOGENS	**RECOMMENDED THERAPY**
Streptococcus pneumoniae *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus* Antibiotic-sensitive enteric gram-negative bacilli *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* species *Proteus* species *Serratia marcescens*	Ceftriaxone, 1-2 g IV/IM every 12-24 hr, maximum of 4 g/day, with duration dependent on clinical response and individualized, as discussed in text *or* Levofloxacin, 500-750 mg IV every day, with duration dependent on clinical response and individualized; or ciprofloxacin, 400 mg IV every 8 hr, with duration dependent on clinical response and individualized; or moxifloxacin, 400 mg IV or orally every 24 hr, with duration dependent on clinical response and individualized *or* Ampicillin-sulbactam, 1.5-3 g (1-2 g ampicillin and 0.5-1 g sulbactam) IV/IM every 6 hr, maximum of 4 g sulbactam/day, depending on type and severity of infection, with duration dependent on clinical response and individualized *or* Ertapenem, 1 g IV/IM once a day, with duration dependent on clinical response and individualized
GROUP B: PATIENTS WITH HAP, VAP, OR HCAP AND WITH LATE-ONSET PNEUMONIA OR WITH RISK FACTORS FOR MDR PATHOGENS	
ORGANISMS	**THERAPY**
Streptococcus pneumoniae *Haemophilus influenzae* Methicillin-sensitive *S. aureus* Antibiotic-sensitive enteric gram-negative bacilli *E. coli* *K. pneumoniae* *Enterobacter* species *Proteus* species *S. marcescens* MDR pathogens *Pseudomonas aeruginosa* *K. pneumoniae* (extended spectrum β-lactamase producing) *Acinetobacter* species Methicillin-resistant *S. aureus* *Legionella pneumophila*	Antipseudomonal cephalosporin (ceftazidime, 2 g IV every 8 hr, or cefepime, 1-2 g every 8-12 hr, with duration dependent on clinical response and individualized) *or* Antipseudomonal carbapenems (meropenem, 1 g every 8 hr, or imipenem, 500 mg every 6 hr or 1 g every 8 hr, with duration dependent on clinical response and individualized) *or* β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam, 4.5 g IV every 6 hr, with duration dependent on clinical response and individualized) *plus* Antipseudomonal fluoroquinolone (levofloxacin, 750 mg IV every day, or ciprofloxacin, 400 mg IV q8h, with duration dependent on clinical response and individualized) *or* Aminoglycoside (amikacin, 15-20 mg/kg/day, divided every 8-12 hours, with monitoring to maintain trough lower than 4-5 μg/mL; or gentamicin, 7 mg/kg/day as a single daily dose, with monitoring to maintain trough levels lower than 1 μg/mL; or tobramycin, 4-7 mg/kg/day as a single daily dose, with monitoring to maintain trough levels lower than 1 μg/mL and duration dependent on clinical response and individualized) *plus* Vancomycin (15 mg/kg IV every 12 hr, with monitoring to maintain trough at 10-15 μg/mL and duration dependent on clinical response and individualized) or linezolid (600 mg IV every 12 hr, with duration dependent on clinical response and individualized)

HAP = hospital-associated pneumonia; HCAP = health care–associated pneumonia; MDR = multidrug resistant; VAP = ventilator-associated pneumonia.
Adapted from American Thoracic Society. Guidelines for management of adults with hospital-acquired ventilator associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005:171:388-416.

H. influenzae, MRSA, and most antibiotic-sensitive gram-negative bacilli, including *E. coli, K. pneumoniae, Proteus* species, *Enterobacter* species, and *Serratia marcescens.*

Late-Onset Disease

In contrast, with late-onset hospital-acquired pneumonia, ventilator-associated pneumonia, or health care–associated pneumonia, or when risk factors for MDR infection have been identified, multiagent regimens should be used initially. Options include an antipseudomonal cephalosporin such as ceftazidime or cefepime, an antipseudomonal carbapenem (meropenem or imipenem), or a β-lactam/β-lactamase inhibitor agent such as piperacillin-tazobactam; in addition, either an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside such as amikacin, gentamicin, or tobramycin should be used. In combination, these agents should empirically address most MDR pathogens, including *P. aeruginosa, Acinetobacter* species, and *K. pneumoniae* strains with extended-spectrum β-lactamase production. Most *L. pneumophila* isolates will also be covered, but if *Legionella* is strongly suspected, a macrolide such as azithromycin should be included. Finally, either vancomycin or linezolid should be added for coverage of MRSA if risk factors are present or the risk for MRSA is high locally.

Duration of Treatment

The initiation of empirical antibiotic therapy mandates careful daily reassessment. If the patient improves over the first 48 to 72 hours, strong consideration should be given to de-escalating antibiotic therapy based on culture results. If lower respiratory cultures remain negative but the patient has not improved, an extrapulmonary site of infection should be considered. Additional radiographic imaging and cultures from the lung, pleura, and other sites may be helpful. The total duration of therapy, therefore, must be individualized. In general, aminoglycoside use should be limited to 5 to 7 days. Overall antibiotic therapy can be as short as 7 days if the patient has improved, but patients with sluggish improvement may require 14 to 21 days of therapy.

PREVENTION

Sources of pathogens for hospital-acquired pneumonia include the environment, health care devices, and transfer of microbes by patients, staff, and visitors. Thus, scrupulous hand hygiene is essential for reducing these infections. Colonization plus aspiration of oropharyngeal pathogens or leakage of secretions around endotracheal tubes is the usual route of inoculation. The stomach and sinuses may be additional sites harboring pathogens. Infected biofilms on endotracheal tubes may also serve as an important reservoir for these infections. In this light, aggressive measures should be enforced to reduce the risk for hospital-acquired pneumonia and ventilator-associated pneumonia. Prevention centers first on staff education and compliance with alcohol-based hand disinfection, which must be used before and after each patient interaction. In addition, patients with documented MDR organisms should be isolated to reduce the risk for patient cross-contamination. Microbiologic surveillance within the hospital environment is also necessary to identify MDR organisms and determine antibiotic use and susceptibility patterns. Within the ICU, intubation and reintubation rates should be monitored and reduced as feasible, the duration of mechanical ventilation should be minimized to reduce the risk for ventilator-associated pneumonia, and methods known to reduce infection rates should be followed (Chapter 105). Ventilator-associated pneumonia can be reduced by elevation of the head of the patient's bed, daily "sedation vacations," daily assessment of the patient's readiness for extubation, peptic ulcer disease prophylaxis, and deep vein thrombosis prophylaxis. In addition, continuous aspiration of subglottic secretions is a safe procedure that also reduces the use of antimicrobial agents and the incidence of ventilator-associated pneumonia in patients who are at risk.■

Grade A

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SUGGESTED READINGS

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