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69 Acute Pneumonia

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SHORT VIEW SUMMARY

Epidemiology and Etiology

- Pneumonia is the most common cause of infection-related death.
- Predominant pathogens of community-acquired pneumonia (CAP) in adults include *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae*.
- *Legionella* species, *Staphylococcus aureus,* and enteric gram-negative bacilli are less frequent causes that can produce more severe disease.
- Predominant pathogens of patients recently hospitalized or nursing home residents include *S. aureus,* aerobic gram-negative rods, including *Pseudomonas aeruginosa,* and mixed aerobic/anaerobic organisms.

Diagnosis

- Typical clinical manifestations are cough—the sine qua non of pneumonia—sputum production, dyspnea, chest pain, fever, fatigue, sweats, headache, nausea, myalgia, and occasionally abdominal pain and diarrhea.
- Gram stain and culture of sputum samples remain valuable diagnostic assays.
- Blood cultures should be obtained in all patients who are immunocompromised, have health care–associated (HCAP) or hospital-acquired pneumonia (HAP), or are hospitalized with severe CAP.
- Chest radiographs should be obtained on all patients with suspected pneumonia.
- Several biomarkers, including procalcitonin and C-reactive protein, are under assessment as discriminatory assays to define populations with a higher likelihood of bacterial infection that could benefit from antibiotic therapy, but the clinical utility of such assays has not yet been established.

Therapy

- One of three severity index scores (PSI, CURB-65, or CRB-65) can be used to assess the need for hospitalization in immunocompetent patients with CAP, and similar indices can be used to define the need for intensive care unit admission.
- Antibiotic therapy for pneumonia should be started as soon as the diagnosis is considered likely.
- Advanced macrolides, respiratory fluoroquinolones, and β-lactam agents are the principal antibiotics used for the treatment of CAP. Coverage for *S. aureus* and mixed anaerobes should be considered in select situations (see Table 69-4 for suggested agents and dosages).
- Antibiotic treatment for HCAP should include coverage for potentially drug-resistant *S. aureus* and aerobic gram-negative bacilli and in most settings includes coverage for *Pseudomonas aeruginosa* (see Table 69-4 for suggested agents and dosages).
- The duration of intravenous treatment, inpatient hospitalization, and total intravenous and oral antibiotic therapy for CAP should be guided by the patient's clinical stability.

Prevention

- Provide immunization as appropriate with influenza and pneumococcal vaccines.
- Encourage cessation of tobacco smoking.

In 1901, Sir William Osler noted in the fourth edition of his book *The Principles and Practice of Medicine* that "the most widespread and fatal of all acute diseases, pneumonia, is now Captain of the Men of Death."[1] Over a century later, the prominence of pneumonia as a clinical entity remains. It remains among the top 10 most common causes of death among all age groups in the United States and the single most common cause of infection-related mortality.[2] The clinical challenge of community-acquired pneumonia (CAP) involves the wide array and ever-increasing number of microbial agents that can cause disease (Table 69-1A-D), the difficulty in making a clinical and etiologic diagnosis, and the fact that no single antimicrobial regimen can cover all the possible causes. Because a specific etiologic diagnosis is often not possible at the time initial treatment is begun, the clinician must decide which empirical therapy is most appropriate. The increasing prevalence of antibiotic resistance among many of the most common pathogens has made this challenge more difficult. An understanding of the pathogenesis of the disease, evaluation of relevant data from a careful history and physical examination, recognition of common clinical patterns of infection, and information from the microbiology laboratory all aid in narrowing down the possible etiologic agents of pneumonia, thereby allowing reasonable therapy to be selected empirically.

HOST DEFENSES AND PATHOGENESIS

The lung is constantly exposed to the mixture of gases, particulate material, and microbes that constitute inspired air. Although the lower respiratory tract has traditionally been considered sterile, recent investigations using culture-independent techniques have shown in normal healthy individuals there is a similar microbiota in the upper and lower respiratory tract, although with a lower concentration of microorganisms within the lung.[3] A more complex microbiota has been demonstrated in individuals with chronic obstructive pulmonary disease and those with cystic fibrosis, and there can be significant variations in the microbiota at different locations within the lungs of individuals.[4,5] The development of acute pulmonary infection appears to arise when there is a defect in host defenses, exposure to a particularly virulent microorganism, or an overwhelming inoculum. Infectious agents gain entry to the lower respiratory tract through aspiration of upper airway resident microbiota, inhalation of aerosolized material, and, less frequently, metastatic seeding of the lung from blood.

Pulmonary Defense Systems

The pulmonary defense system involves both innate and adaptive immunity, including anatomic and mechanical barriers, humoral immunity, cell-mediated immunity, and phagocyte activity (Table 69-2).[6,7] The upper airways, including the nasopharynx, oropharynx, and larynx, are the sites first exposed to inhaled microorganisms. The nasal mucosa contains ciliated epithelium and mucus-producing cells. Mechanical clearance of entrapped organisms occurs through the nasopharynx via expulsion or swallowing. In the oropharynx, the flow of saliva, sloughing of epithelial cells, local production of complement, and bacterial interference from resident microbiota serve as important factors in local host defense. Secretory immunoglobulin A (IgA) is the major immunoglobulin produced in the upper airways and accounts for 10% of the total protein of nasal secretions. It possesses antibacterial and antiviral activity despite being a relatively poor opsonin. Despite some controversy, low IgA levels are probably not associated with increased bacterial infection. IgG and IgM enter the airways predominantly via transudation from the blood. Their roles in bacterial opsonization, complement activation, agglutination, and neutralization activity are similar to those noted in serum.

KEYWORDS

aspiration; bronchoscopy; *Chlamydia pneumoniae*; CRB-65; *Legionella pneumophila*; *Mycoplasma pneumoniae*; pneumonia; pneumonia severity index (PSI); procalcitonin; *Streptococcus pneumoniae*

TABLE 69-1A Causative Agents of Acute Pneumonia: Bacteria

COMMON	UNCOMMON
Streptococcus pneumoniae	*Acinetobacter* spp.
Staphylococcus aureus	*Actinomyces* and *Arachnia* spp.
Haemophilus influenzae	*Bacillus* spp.
Mixed anaerobic bacteria (aspiration)	*Moraxella catarrhalis*
Bacteroides spp.	*Campylobacter fetus*
Fusobacterium spp.	*Eikenella corrodens*
Peptostreptococcus spp.	*Francisella tularensis*
Peptococcus spp.	*Neisseria meningitidis*
Prevotella spp.	*Nocardia* spp.
Enterobacteriaceae	*Pasteurella multocida*
Escherichia coli	*Proteus* spp.
Klebsiella pneumoniae	*Burkholderia pseudomallei*
Enterobacter spp.	*Salmonella* spp.
Serratia spp.	*Enterococcus faecalis*
Pseudomonas aeruginosa	*Streptococcus pyogenes*
Legionella spp. (including *L. pneumophila* and *L. micdadei*)	

TABLE 69-1B Causative Agents of Acute Pneumonia: Viruses

CHILDREN	ADULTS
Common	**Common**
Respiratory syncytial virus	Influenza A virus
Parainfluenza virus types 1, 2, 3	Influenza B virus
Influenza A virus	Respiratory syncytial virus
Influenza B virus	Human metapneumovirus
Rhinovirus	Adenovirus types 4 and 7 (in military recruits)
Bocavirus	Rhinovirus
Human metapneumovirus	
Uncommon	**Uncommon**
Adenovirus types 1, 2, 3, 5, 14	Coxsackievirus
Coxsackievirus	Echovirus
Echovirus	Coronavirus (SARS, MERS-CoV)
Hantavirus	Hantavirus
Measles virus	Epstein-Barr virus
Coronavirus (SARS, MERS-CoV)	Cytomegalovirus
	Parainfluenza virus
	Herpes simplex virus
	Human herpesvirus 6
	Varicella-zoster virus

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS, severe acute respiratory syndrome.

TABLE 69-1C Causative Agents of Acute Pneumonia: Fungi

COMMON	UNCOMMON
Histoplasma capsulatum	Agents of mucormycosis
Coccidioides immitis	*Rhizopus* spp.
Cryptococcus neoformans	*Absidia* spp.
Aspergillus spp.	*Mucor* spp.
	Cunninghamella spp.
	Candida spp.

TABLE 69-1D Causative Agents of Acute Pneumonia: Other Agents

Rickettsia
Coxiella burnetii
Rickettsia rickettsiae
Mycoplasma, Chlamydia
Mycoplasma pneumoniae
Chlamydia psittaci
Chlamydia trachomatis
Chlamydia pneumoniae (TWAR)
Mycobacteria
Mycobacterium tuberculosis
Nontuberculous Mycobacteria
M. abscessus
M. avium-intracellulare complex
M. kansasii
M. chelonae
M. fortuitum
M. xenopi
M. simiae
M. scrofulaceum
M. malmoense
M. seoulense
Parasites
Ascaris lumbricoides
Pneumocystis jirovecii
Strongyloides stercoralis
Toxoplasma gondii
Paragonimus westermani

Adherence of microorganisms to epithelial surfaces of the upper airways is a critical initial step in colonization and subsequent infection. Changes in fibronectin secretion and in binding characteristics of epithelium for various lectins occur as a response to underlying diseases. This may help to explain why colonization occurs in some clinical settings and not in others. Particles greater than 10 µm are efficiently filtered by the hair in the anterior nares or impact onto mucosal surfaces because of the configuration of the upper airways and the nasal turbinates. The cough and epiglottic reflexes also keep large particulate matter from reaching the central airways. The trachea and conducting airways of the transbronchial tree are usually effective in entrapping particles from 2 to 10 µm. The sharp angles at which the central airways branch cause particles to impact on mucosal surfaces, where they are entrapped by endobronchial mucus. Once entrapped, particles are removed by ciliated epithelium to the oropharynx.

Epithelial cells, which line the conducting airways, submucosal glands, and alveoli, produce airway surface liquid, which is a complex mixture of proteins and peptides mixed with plasma transudate. Airway surface liquid contains lysozyme, lactoferrin, and secretory leukocyte proteinase inhibitor, all of which possess microbicidal activity.[8] Respiratory epithelial cells produce other potent antimicrobial peptides, including cathelicidins and β-defensins. These peptides possess individual antimicrobial activity as well as synergistic antimicrobial activity with each other. In addition, the β-defensins may act as chemokines for memory T cells and dendritic cells, thereby serving as a link between the innate and adaptive immune systems.

Most bacteria are 0.5 to 2 µm. This size particle may reach the terminal airways and alveoli. No mucociliary apparatus exists at this level, yet a variety of humoral and cell-mediated host defenses function here. The alveolar-lining fluid contains surfactant, fibronectin, IgG, and complement, all of which are effective opsonins. Surfactant is composed of several components (SP-A, SP-B, SP-C, SP-D) that serve to increase the microbicidal capacity of macrophages. These compounds may also affect free-radical production and lymphocyte activity.[9] SP-A and SP-D are collectins, which are a family of collagenous carbohydrate-binding proteins. These proteins bind a variety of organisms, including viruses, gram-negative and gram-positive bacteria, mycobacteria, and fungi, which may decrease their virulence or enhance phagocytosis by neutrophils and alveolar macrophages.[10] Free fatty acids, lysozyme, iron-binding proteins, and defensins are also present and may be directly microbicidal.

Phagocytic cells including macrophages and neutrophils play a major role in pulmonary host defense. Four distinct populations of macrophages exist in the lung and vary in their location and function.[11,12] The alveolar macrophage is located in the alveolar-lining fluid at the interphase between air and lung tissue. It serves as the resident phagocytic cell in the lower airway and is the first phagocyte encountered by inert particles and potential pathogens entering the lung via inspired air. Alveolar macrophages play several critical roles.[7] As phagocytic cells, they can eliminate certain organisms. If the numbers

TABLE 69-2 Pulmonary Host Defenses

LOCATION	HOST DEFENSE MECHANISM*
Upper Airways	
Nasopharynx	Nasal hair
	Turbinates
	Anatomy of upper airways
	Mucociliary apparatus
	IgA secretion
Oropharynx	Saliva
	Sloughing of epithelial cells
	Cough
	Bacterial interference
	Complement production
Conducting Airways	
Trachea, bronchi	Cough, epiglottic reflexes
	Sharp-angled branching of airways
	Mucociliary apparatus
	Airway surface liquid (lysozyme, lactoferrin, secretory leukocyte proteinase inhibitor, antimicrobial peptides)
	Dendritic cells† / Bronchus-associated lymphoid tissue } Antigen processing and presentation→stimulation of memory and effector T cells and B cells
	Immunoglobulin production (IgG, IgM, IgA)
Lower Respiratory Tract	
Terminal airways, alveoli	Alveolar lining fluid (surfactant, fibronectin, immunoglobulin, complement, free fatty acid, iron-binding proteins)
	Alveolar macrophages / Interstitial macrophages
	Neutrophil recruitment‡ (pattern recognition receptors→transcription factor stimulation→proinflammatory and anti-inflammatory cytokine and chemokine production)
	Dendritic cells† / Bronchus-associated lymphoid tissue } Antigen processing and presentation→stimulation of memory and effector T cells and B cells

*Aspects of native and adaptive immunity play a role throughout the respiratory tract.
†Major component of adaptive immunity and important in response to vaccines and prior infections.
‡Major component of innate immunity.

of organisms increase beyond the macrophages' capability to handle them or if the organisms involved are particularly virulent (e.g., *Pseudomonas aeruginosa*), the macrophage becomes a mediator of an inflammatory response by producing cytokines that recruit neutrophils into the lung.[13] Interstitial macrophages are located in the lung connective tissue and serve as both phagocytic cells and antigen-processing cells. Dendritic cells derive from monocytes and are located within the epithelium of the trachea, conducting airways, terminal airways, alveolar septa, pulmonary vasculature, and visceral pleura. These cells are therefore positioned to interact with antigens in inhaled air. Dendritic cells (and a specialized subpopulation termed *Langerhans cells*) possess an enhanced capacity to capture, process, and present class II antigens. They can migrate to lymphoid tissue, where they can stimulate T-cell immune responses. Dendritic cells can also produce a variety of cytokines and chemokines, including interleukin (IL)-12, which serves to stimulate B-cell immune function.[14] The intravascular macrophage is located in the capillary endothelial cells. These cells are actively phagocytic and remove foreign or damaged material entering the lungs via the bloodstream.

Neutrophil recruitment is crucial for the inflammatory response in the lung. The mechanisms involved in the initial detection of organisms in the lung and the generation and subsequent resolution of a response to them are now being more clearly delineated.[15-20] Other lung parenchymal cells may also help regulate the inflammatory response.[21] In addition to epithelial cells, interstitial macrophages, and dendritic cells, endothelial cells, pulmonary smooth muscle cells, and fibroblasts produce both proinflammatory (e.g., colony-stimulating factors, chemokines) and anti-inflammatory (IL-10) factors.

Microorganisms express molecular recognition patterns that are unique and different from that of the host. Pattern recognition receptor families such as Toll-like receptors are present on epithelioid cells, alveolar macrophages, dendritic cells, as well as other cells that are located in strategic areas of the lung and either individually or in groups serve to recognize molecular patterns of invading organisms.[21] This recognition leads to the generation of early-response cytokines such as tumor necrosis factor-α (TNF-α) and IL-I that then activate transcription factors such as mitogen-activated protein kinase, phosphoinositide 3-kinase, nuclear factor kappa B (NF-κB), and interferon-regulatory factors. These transcription factors serve as a common pathway for pattern recognition receptors and orchestrate the development of the inflammatory response by mediating the transcription of chemokines, adhesin molecules, and other cytokines. This signal cascade serves two purposes. The first is to generate and maintain the inflammatory response to recruit neutrophils into areas of microbial invasion. The other goal is to activate anti-inflammatory response mediators, which lead to the shedding of receptors, neutralization of cytokines, and inhibition of macrophage recruitment, which all serve to ensure that the inflammatory response is held in check and that noninvolved areas of lung are not injured. It is this balance of pro-inflammatory and anti-inflammatory cytokines and effector molecules that allows for sterilization of an infected area of lung without gross destruction of the lung itself. In addition, it is now recognized that polymorphisms and defects are not uncommonly found for both pattern recognition receptors and the inflammatory and anti-inflammatory mediators and that these genetic variations can contribute to an individual's susceptibility to pneumonia.[20]

Cell-mediated immunity via lymphocytes and macrophages is central to adaptive immune responses in the lung and is especially important against certain pathogens, including viruses and intracellular organisms that can survive within pulmonary macrophages (e.g., *Mycobacterium, Legionella*).[12] Lymphocytes within the lung are found along the epithelial surfaces (LES), as well as within the interstitial and intravascular spaces. LES cells are predominantly memory T cells and interact both with epithelial cells and dendritic cells. Interstitial cells are similarly predominantly T cells but with a different CD4/CD8 ratio than seen with that of either LES cells or intravascular lymphocytes

and with an abundance of natural killer cells. In addition, although uncommon in adults, in childhood there are organized lymphoid tissue collections in the lung located in follicles along the bronchial tree termed *bronchus-associated lymphoid tissue* (BALT) collections. BALT collections appear to be morphologically similar to Peyer's patches in the intestine and are similarly associated with both the vasculature and the mucosal epithelium. Inhaled antigens therefore are able to cross the epithelial surface and immediately encounter cells involved with antigen processing. Once these antigens are processed and presented, B and T lymphocytes localize and are stimulated to become memory cells and effector cells, with antibody production occurring in this tissue.

Antigens inhaled into the alveolus and captured by antigen-presenting cells subsequently activate intra-alveolar lymphoid cells. These cells can stimulate the migration of memory lymphocytes into the area, leading to a localized accumulation of antigen-specific T and B lymphocytes, many of which possess effector cell function. As is true in other anatomic areas, binding of T cells to endothelium is a critical first step in the inflammatory process and is mediated by the interaction of leukocyte function–associated antigen (LFA)-1 integrins on the lymphocyte cell surface with ligands exposed by endothelium in areas of inflammation (intercellular adhesion molecules 1 and 2 and vascular cell adhesion molecule 1). Expression of these ligands on pulmonary endothelium is upregulated by inflammatory mediators such as IL-1, interferon-γ, and TNF-α, as well as by bacterial lipopolysaccharides.

Lymphocytes in the lung have several major roles in the lung, including the production of antibody, cytotoxic activity (including killing of virally infected cells), production of inflammatory mediators, and mediation of immune tolerance. The lung contains a variety of cytotoxic T cells, including natural killer cells (antigen nonrestricted), antibody-dependent cytotoxic cells, and antigen-restricted cytotoxic cells. Pulmonary T cells produce a large number of cytokines. Mouse models suggest that unstimulated T cells produce mainly IL-2. After stimulation and conversion to memory T cells, two distinct groupings of cytokines are produced. The helper T-cell 1 (Th1) and 2 (Th2) pattern of cytokine production noted in murine models occurs in humans, although it appears to be less restrictive. Th1 cells produce interferon-γ, IL-2, IL-6, and IL-10 and contribute to cell-mediated immunity, whereas Th2 cells produce IL-4, IL-5, IL-10, and IL-13 and contribute to humoral immune function. Furthermore, IL-3, TNF-α, granulocyte-macrophage colony-stimulating factor, and chemokines are secreted by both Th1 and Th2 phenotypes. Th1 cells are involved in cell-mediated inflammatory reactions, whereas Th2 cells stimulate antibody production, especially IgE, and stimulate eosinophil activity. However, there appears to be both Th1 and Th2 responses in many immune responses. The interaction of T-regulatory cells with mucosal dendritic cells appears to mediate the phenomenon of immune tolerance in the lung.

Impairment of Pulmonary Defenses

The defenses of the lung, when they are functioning normally, are extremely efficient in maintaining low microbial concentrations in the lower airways. However, a number of factors are known to interfere with these defenses and predispose the host to infection. Alterations in the level of consciousness from any cause (stroke, seizures, drug intoxication, anesthesia, alcohol abuse, and even normal sleep) can compromise epiglottic closure and lead to aspiration of oropharyngeal microbiota into the lower respiratory tract.[22] Cigarette smoke, perhaps the most common agent involved in compromising natural pulmonary defense mechanisms, disrupts mucociliary transport as well as altering macrophage B- and T-lymphocyte functionality.[23,24]

Alcohol not only impairs the cough and epiglottic reflexes but also has been associated with increased colonization of the oropharynx with aerobic gram-negative bacilli, decreased mobilization of neutrophils, abnormal phagocyte oxidative metabolism, and abnormal chemotaxis.[25,26] Alcohol effectively blocks the TNF response to endotoxin, with decreased recruitment of neutrophils to the lung. Furthermore, alcohol enhances monocyte production of 1L-10, a cytokine with anti-inflammatory properties.[27]

Infections with *Mycoplasma pneumoniae* or *Haemophilus influenzae* may interfere with normal ciliary function.[28] Viruses may actually destroy respiratory epithelium and may disrupt normal ciliary activity. Neutrophil function, including chemotaxis, phagocytosis, and stimulation of oxidative metabolism and alveolar macrophage function, may also be inhibited by certain viral infections.[29] Sepsis associated with extrapulmonary infections may undermine lung defense mechanisms. In animal models, exposure to lipopolysaccharide or endotoxin decreases lung clearance of a bacterial challenge.[30] Infection with human immunodeficiency virus (HIV) compromises many of the components of pulmonary host defense. Quantitative defects involve the naïve CD4 T cells initially, with the memory CD4 T cells depleted more rapidly later in infection. Functional defects caused by the virus include impaired response to remote recall antigens, inhibited response to soluble antigen followed in time by decreased T-cell response to alloantigens and mitogens, impaired IL-2 and interferon-γ production, and decreased immunoglobulin production.[31] In BALT, destruction of dendritic cells and degeneration of lymphoid follicles have been noted. Defective antigen presentation by dendritic cells has also been observed. Abnormal chemotaxis, phagocytosis, and oxidative metabolism in neutrophils of patients with acquired immunodeficiency syndrome (AIDS) have been described.

Iatrogenic manipulations that bypass or interfere with the usual host defenses of the upper airways (endotracheal tubes, nasogastric tubes, and respiratory therapy machinery) all predispose to infection.[32] A variety of commonly prescribed drugs including aspirin, erythromycin, and aminophylline have been shown to alter host defenses in vitro or in models, but the clinical significance of this is uncertain.[33,34] Recent data with macrolides suggest that they have immunomodulatory activity that could have beneficial effects in some settings.[35] Other classes of agents, including proton pump inhibitors, histamine type 2 (H2) receptor antagonists, and antipsychotic agents, have been associated with pneumonia in population-based studies, although the associations have been challenged and the exact pathophysiologic mechanisms have not been determined.[36-38]

Other factors that impair pulmonary host defenses include hypoxemia, acidosis, toxic inhalations, pulmonary edema, uremia, malnutrition, immunosuppressive agents, and mechanical obstruction.[39-41] Recent clinical studies have also shown an increased risk for pneumonia with therapeutic hypothermia now being used for management of cardiac arrest and head trauma.[42]

Older adults are at increased risk for the development of pneumonia (see Chapter 315). Although numerous factors play an important role in this regard, including an increased number and increased severity of underlying diseases and an increased number of hospitalizations, there are age-related impairments in host defenses.[43] Less effective mucociliary clearance and abnormal elastic recoil may lead to less effective coughing and clearing of the upper airways. Some populations of elderly patients have an increased incidence of microaspiration. Changes in humoral immunity and cell-mediated immune function have been documented in older persons, although their role in the development of infection remains unclear. Immune dysregulation has been shown to occur in the elderly such that low-grade inflammation occurs in the lung in the absence of clinically detectable infection.[44]

Recurrent episodes of bacterial pneumonia suggest the presence of specific predisposing factors.[45] In children and young adults, recurrent pneumonia is associated with defects in host defenses, including recurrent aspiration, asthma, congenital cardiac or pulmonary disease, and altered immune function.[46-49] Congenital defects in ciliary activity and cystic fibrosis are other clinical entities associated with recurrent pneumonia in young persons.[50,51] Structural lung abnormalities such as bronchiectasis and pulmonary sequestration are also important predisposing factors for both younger and older patient populations. As more has become known about the molecular basis of the inflammatory response, it has become clear that a variety of genetic polymorphisms exist that are associated with predisposition to the development of pneumonia. It is important to recognize that these defects may be associated with a narrow range of potential pathogens, which may aid in the identification of the defect.[17,20]

Although most congenital defects in host defenses appear in childhood, common variable hypogammaglobulinemia may first appear in adulthood with recurrent pneumonia. Acquired host defense defects

are more varied and include malignancies (lymphoma, chronic lymphocytic leukemia, multiple myeloma), infection (AIDS), and iatrogenic causes (immune suppression associated with solid-organ or marrow transplantation, cancer chemotherapy, high-dose corticosteroid treatment, and TNF inhibitors). Underlying respiratory tract disorders such as chronic obstructive pulmonary disease (COPD), bronchiectasis, adult-onset cystic fibrosis, bronchopulmonary sequestration, and tracheobronchomegaly may present as pneumonia. Bronchial obstruction due to intrinsic compression (adenocarcinoma) or extrinsic compression (lymphadenopathy due to sarcoidosis or malignancy) has also been associated with recurrent episodes of pneumonia. Underlying diseases that predispose to aspiration lead to an increased incidence of pneumonia. These may be associated with gastrointestinal diseases (tracheoesophageal fistula, esophageal diverticula, esophageal reflux, esophageal stricture), neuromuscular disorders (myasthenia gravis, dementia, amyotrophic lateral sclerosis), and cancer of the head and neck. Most systemic illnesses, including chronic renal failure, diabetes, and sickle cell disease, have been associated with pneumonia.

CLINICAL EVALUATION

History

The history should attempt to define (1) symptoms consistent with the diagnosis of pneumonia, (2) the clinical setting in which the pneumonia takes place, (3) defects in host defense that could predispose to the development of pneumonia, and (4) possible exposures to specific pathogens.

Respiratory symptoms are commonly encountered in primary care practices but are usually not associated with pneumonia. Analysis of data over 9 years from 1980 to 1994 found that between 5 and 10 million primary care visits each year were for cough, with only 4% to 6% of these visits linked to pneumonia.[52] Therefore, a serious effort should be made to differentiate pneumonia from other clinical entities with which it may be confused. The predominant clinical findings of pneumonia related to the respiratory tract should be sought, including cough, sputum production, dyspnea, chest pain, and fever.[53] It should also be recognized that nonrespiratory symptoms are commonly present, including fatigue, sweats, headache, nausea, and myalgia, and occasionally abdominal pain and diarrhea.[54] With increasing age, both respiratory and nonrespiratory symptoms of pneumonia become less frequent. Unfortunately, symptoms at presentation elucidated by a careful history may not always be able to distinguish pneumonia from other respiratory problems.

Specific etiologic agents of pneumonia have been associated with certain underlying diseases and patient populations. Pneumonia due to *M. pneumoniae* occurs more often in younger people, but it may be a cause of pneumonia in older patients severe enough to require hospitalization.[55] Gram-negative bacterial pneumonia tends to occur in older adults, especially those who are debilitated with comorbid diseases or are ill enough to require management in an intensive care unit (ICU). Tuberculosis should be suspected in the homeless, those infected with HIV, those who come from developing countries where tuberculosis is prevalent, and those who have been exposed to others with the disease. Staphylococcal pneumonia classically has been noted during epidemics of influenza.[56] Over the past 20 years, methicillin-resistant *Staphylococcus aureus* (MRSA) has grown in importance as a cause of ventilator-associated pneumonia (VAP). In addition, since the late 1990s, strains of community-acquired MRSA have emerged as infrequent but important causes of CAP.[57,58]

Pneumonia has been noted to occur with increased frequency in patients with a variety of underlying disorders such as congestive heart failure, diabetes, alcoholism, and COPD. In one series of 292 patients with pneumonia, only 18% were found to have no underlying disease.[59] Certain lifestyle factors have also been associated with an increased risk for pneumonia. These include cigarette smoking; alcohol use, especially in males; contact with children and pets; and living in a household with more than 10 people.[60] Viral upper respiratory tract infections can predispose to pneumonia and may be associated with more severe disease.[61,62] Recent dental manipulations, sedative overdoses, seizures, alcoholism, or loss of consciousness for any reason should raise the suspicion for anaerobic infection caused by aspiration of oral contents.[22]

Special note needs to be made of the relationship between pneumonia and patients with COPD.[63] Although well-controlled studies are lacking, it does appear that patients with COPD have an increased incidence of pneumonia. However, because the tracheobronchial tree is often colonized with *Streptococcus pneumoniae* and *H. influenzae,* it has been difficult to distinguish clearly between colonization and infection in many studies. Although these organisms play an important role as etiologic agents of pneumonia in this patient population, most of the clinical studies were carried out before it was recognized that other, less common pathogens also play a significant role in causing disease. The roles of *Moraxella catarrhalis, Legionella, Chlamydia,* and aerobic gram-negative rods including *P. aeruginosa* have been established.[63-65] Cystic fibrosis is commonly associated with *Pseudomonas* and staphylococcal pulmonary infections.[51] *Burkholderia* spp., *Stenotrophomonas* spp., *Achromobacter xylosoxidans,* and atypical mycobacteria are also important pulmonary pathogens in this setting. Pulmonary alveolar proteinosis can be associated with *Nocardia* infection.

Patients infected with HIV are at high risk for the development of pulmonary infections.[66-69] Although the incidence of pneumonia has decreased notably in the developed world with the advent of highly active antiretroviral therapy, pneumonia remains a common HIV complication. Principal risk factors for pneumonia in this population include low current $CD4^+$ count, nadir $CD4^+$ count, injection drug use, smoking, increasing age, and lack of highly active antiretroviral therapy and anti-*Pneumocystis* prophylaxis.[67,70] In considering the etiology of pulmonary infection in patients infected with HIV, geographic exposures, demographic characteristics of the patient, and the degree of immune suppression need to be considered. With the development of highly active antiretroviral therapy (HAART) and effective prophylactic strategies, the incidence of *Pneumocystis jirovecii* pneumonia in patients with AIDS has decreased from 70% to 80% to less than 1 per 100 patient-years.[71] It is now predominantly seen in individuals who have a $CD4^+$ count less than $100/mm^3$ and are either unaware of having HIV infection or are not receiving care.[69] Bacterial pneumonia was a significant complication for HIV-infected individuals and in the pre-antiretroviral era with an incidence 5- to 10-fold that seen in the general population; and the incidence of invasive pneumococcal disease is more than 50-fold higher in HIV-infected patients than in non–HIV-infected controls.[70,72] The incidence of these infections has now notably decreased, although there remains a high risk in patients not on treatment.[69] The incidence of pneumonia due to *P. aeruginosa* and *S. aureus* has also been notably higher in HIV-infected patients.[69] Although relatively less common in the developed world, in developing countries, *Mycobacterium tuberculosis* is now viewed as the major pulmonary pathogen in patients with AIDS.[68] The use of HAART has led to a decreased incidence of AIDS, but its overall importance as a pulmonary pathogen remains. In the severely immunosuppressed HIV population, fungal infections can play a major role, and depending on the patient's exposure history, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis should be considered.

In patients infected with HIV, the relationship between the degree of immune suppression using the $CD4^+$ count as a marker and the specific etiology of pneumonia deserves emphasis. Bacterial pneumonia and pulmonary tuberculosis usually occur when the $CD4^+$ count is less than 400/μL, with increased risk when the count falls below 200 cells/μL.[73] *Pneumocystis* and disseminated tuberculosis are associated with $CD4^+$ counts below $200/mm^3$, and disseminated nontuberculous mycobacterial and fungal infections occur with $CD4^+$ counts less than 50 to $100/mm^3$.[73] Pulmonary infections in HIV-infected patients are discussed in more detail in Chapter 125.

Pneumonia developing in hospitalized patients often involves Enterobacteriaceae, *P. aeruginosa,* and *S. aureus,* organisms that are unusual in community-acquired disease.[74] Pneumonia in older adults, especially those who are bedridden or who have chronic diseases, had been believed to be more often associated with gram-negative bacilli than is pneumonia in younger populations, but this association remains unclear.[75,76] In general, elderly patients most frequently have infection due to *S. pneumoniae,* nontypeable strains of *H. influenzae, M. catarrhalis,* or aspiration pneumonia.

Recently, it has been recognized that patients with outpatient contact with the health care system develop pneumonia with etiologic

TABLE 69-3 Pneumonia: Etiology Suggested by Exposure History

EXPOSURE HISTORY	INFECTIOUS AGENT
Exposure to concurrent illness in school dormitory or household setting	*Neisseria meningitidis, Mycoplasma pneumoniae*
Environmental Exposures	
Exposure to contaminated aerosols (e.g., air coolers, hospital water supply)	Legionnaires' disease
Exposure to goat hair, raw wool, animal hides	Anthrax
Ingestion of unpasteurized milk	Brucellosis
Exposure to bat droppings (caving) or dust from soil enriched with bird droppings	Histoplasmosis
Exposure to water contaminated with animal urine	Leptospirosis
Exposure to rodent droppings, urine, saliva	Hantavirus
Potential bioterrorism exposure	Anthrax, plague, tularemia
Zoonotic Exposures	
Employment as abattoir work or veterinarian	Brucellosis
Exposure to cattle, goats, pigs	Anthrax, brucellosis
Exposure to ground squirrels, chipmunks, rabbits, prairie dogs, rats in Africa or southwestern United States	Plague
Hunting or exposure to rabbits, foxes, squirrels	Tularemia
Bites from flies or ticks	Tularemia
Exposure to birds (parrots, budgerigars, cockatoos, pigeons, turkeys)	Psittacosis
Exposure to infected dogs and cats	*Pasteurella multocida,* Q fever *(Coxiella burnetii)*
Exposure to infected goats, cattle, sheep, domestic animals, and their secretions (milk, amniotic fluid, placenta, feces)	Q fever *(C. burnetii)*
Travel Exposures	
Residence in or travel to San Joaquin Valley, southern California, southwestern Texas, southern Arizona, New Mexico	Coccidioidomycosis
Residence in or travel to Mississippi or Ohio river valleys, Caribbean, central America, or Africa	Histoplasmosis, blastomycosis
Residence in or travel to southern China	SARS, avian influenza
Residence in or travel to Arabian peninsula	MERS-CoV
Residence in or travel to Southeast Asia	Paragonimiasis, melioidosis
Residence in or travel to West Indies, Australia, or Guam	Melioidosis

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS, severe acute respiratory syndrome.

agents that may be seen in both CAP and nosocomial pneumonia.[77,78] Increased importance of MRSA, aerobic gram-negative rods including *P. aeruginosa,* and mixed aerobic/anaerobic organisms due to aspiration are associated with this new syndrome of health care–associated pneumonia (HCAP) (see further discussion under "Pneumonia Syndromes").

Important aspects of a patient's history that may suggest specific potential infectious agents include occupational, animal, and travel history (Table 69-3). A carefully obtained history may also suggest the presence of noninfectious pulmonary disease, such as tumors, sarcoidosis, granulomatosis with polyangiitis (previously known as Wegener's granulomatosis), or pulmonary emboli; all may masquerade as pneumonia.

Physical Examination

Most, but not all, patients with pneumonia look ill, sometimes acutely. They may be breathing with accessory muscles. Elderly patients may appear apathetic. Fever is reported to be present in 65% to 90% of patients with pneumonia. It may be sustained, remittent, or at times hectic. Fever patterns per se, however, are not useful for establishing a specific diagnosis. Oral temperature assessment should be avoided to reduce error caused by rapid mouth breathing. Recording of postural changes in blood pressure and pulse rate is useful in assessing hydration and intravascular fluid volume. The pulse usually increases by 10 beats/min for every degree (centigrade) of temperature elevation. A pulse-temperature deficit (e.g., a relative bradycardia for the amount of fever) should suggest viral infection, mycoplasmal infection, chlamydial infection, tularemia, or infection with *Legionella*. Cyanosis, a rapid respiratory rate, the use of accessory muscles of respiration, sternal retraction, and nasal flaring suggest serious respiratory compromise.

Cutaneous abscesses or "track marks" from injection drug use may signal a source of bacteremia with subsequent pneumonia via hematogenous spread. Bullous myringitis is an infrequent but significant finding in mycoplasmal pneumonia. The presence of poor dentition should suggest a mixed infection due to aspiration of anaerobes and aerobes that colonize the oropharynx. Although edentulous patients may develop anaerobic pneumonia as a result of aspiration, it is uncommon.[79]

Examination of the thorax may reveal "splinting," or an inspiratory lag on the side of the lesion, that is suggestive of bacterial pneumonia. Early in the disease process, definite signs of pulmonary involvement may be lacking or may be manifest only as fine rales. Chest examination may reveal these early signs of pneumonia even though the chest radiograph is normal. Evidence of consolidation (dullness on percussion, bronchial breath sounds, and E to A changes) is highly suggestive of bacterial infection but may be absent in two thirds of patients ill enough to be hospitalized and may be absent more often in patients treated as outpatients.[80] Patients with mycoplasmal or viral infection may exhibit few abnormalities on physical examination despite the presence of impressive infiltrates on the chest radiograph.

The overall usefulness of the history and physical examination to detect the presence of pneumonia has been questioned.[81] The probability of detecting pneumonia varies with the patient population, the prevalence of pneumonia in that population, the threshold values for defining a vital sign as abnormal, and the ability of the clinician to detect abnormal physical findings. However, a great deal of interobserver variation has been shown to exist. In one series, three examiners seeing the same patients could not consistently agree on the physical examination findings. The diagnosis of pneumonia could be made with a sensitivity of only 47% to 69% and with a specificity of 50% to 75%.[81]

Rare findings such as egophony and asymmetrical chest movements have a high predictive value for pneumonia but occur so infrequently that they are of limited utility. Several studies have assessed the utility of clinical prediction rules for the presence or absence of pneumonia based on multiple physical findings.[53] The absence of any vital sign abnormalities (i.e., respiratory rate >20 breaths/min, heart rate >100 beats/minute, and temperature >37.8°C [100°F]) has been associated with a less than 1% chance of a patient's having pneumonia, assuming a pneumonia prevalence of 5% in the population under study. In contrast, a constellation of cough, fever, tachycardia, decreased breath sounds, and crackles raises the possibility of pneumonia being present to between 40% and 50%. Therefore, although variable and nondefinitive, a complete history and physical examination may be extremely helpful in guiding the workup of pneumonia.

Diagnostic Testing

Clinical features derived from a careful history and physical examination, and confirmed by radiographic imaging of the chest that shows a pulmonary infiltrate, suggest the presence of pneumonia. The role of microbiologic tests to identify the specific cause is an important, although controversial, element of care. Most empirical antibiotic regimens are successful in the therapy for CAP, especially mild to moderate cases. Studies comparing empirical therapy with laboratory-guided pathogen-directed care have shown no differences in efficacy, although increased side effects were noted in the patients receiving empirical therapy.[82] Efforts to determine the specific cause of CAP are justified by the fact that they (1) may enable the clinician to narrow the antibiotic spectrum by using fewer agents, thereby decreasing exposure of the patient to potential side effects and potentially reducing the development of resistance; (2) may aid in the specific antibiotic choice for an individual patient depending on the specific epidemiology of infection and the specific resistance patterns of the locale; and (3) may identify pathogens not usually suspected and therefore not

usually covered by empirical therapy. On a broader scale, identifying specific causes may help define new agents, trends in antibiotic resistance in established agents, and epidemiology of infectious outbreaks. The combined use of the standard microbiologic testing in conjunction with nucleic amplification assays can now define the etiology of CAP in up to 89% of cases.[83] The most recent guidelines from the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) have suggested diagnostic testing "whenever the result is likely to change individual antibiotic management" or in patients in whom "the diagnostic yield is thought to be greatest."[84]

Sputum Examination and Examination of Other Respiratory Tract Samples

Microscopic examination and culture of expectorated sputum remain the mainstays of the laboratory evaluation of pneumonia despite ongoing controversy concerning their sensitivity and specificity. Of patients admitted to the hospital with CAP, 40% to 60% will not be able to produce sputum. Of those that do, between 40% to 60% of samples may be judged to be inadequate for further study because of oropharyngeal contamination.[85,86] Many patients have received antibiotics before the studies are carried out, which drastically reduces the diagnostic yield. A variety of organisms cannot be detected by Gram stain, including *Legionella* spp., *Mycoplasma* spp., and *Chlamydia* spp. However, in patients who produce sputum of adequate quality to be examined (minimal or no oropharyngeal contamination), and who have not received prior antibiotics, diagnostic yields of 80% for sputum Gram stain have been reported in the small fraction of patients with bacteremic *S. pneumoniae* pneumonia.[87] Despite its pitfalls, the sputum Gram stain is noninvasive, can be performed no risk to the patient, and under the right circumstances may aid in the diagnosis and choice of empirical therapy in patients with CAP.[88,89]

Examination of the sputum should include observation of the color, amount, consistency, and odor of the specimen. Mucopurulent sputum is most commonly found with bacterial pneumonia or bronchitis. However, sputum of a similar nature has been described in one third to one half of patients with mycoplasmal or adenovirus infections.[90] Scant or watery sputum is more often noted with these and other atypical pneumonias. "Rusty" sputum suggests alveolar involvement and has been most commonly (although not solely) associated with pneumococcal pneumonia.[91] Dark red, mucoid sputum (currant-jelly sputum) suggests Friedlander's pneumonia caused by encapsulated *Klebsiella pneumoniae* (Fig. 69-1).[92] Foul-smelling sputum is associated with mixed anaerobic infections most commonly seen with aspiration.[79]

To maximize the diagnostic yield of the sputum examination, only samples with minimal oropharyngeal contamination should be reviewed. Although there are no definitive guidelines, the number of neutrophils and epithelial cells should be quantitated under low power (×100), with further examination reserved for samples containing 25 or more neutrophils and 10 or fewer epithelial cells.[93] Samples with more epithelial cells and fewer neutrophils are usually nondiagnostic and should be discarded. The morphologic and staining characteristics of any bacteria seen should be recorded and an estimate made of the predominant organisms (Figs. 69-2 to 69-6). When no bacterial predominance exists, this should be noted as well.

In the appropriate clinical setting, a predominance of gram-positive, lancet-shaped diplococci should suggest pneumococcal infection (see Fig. 69-2). When strict criteria for Gram stain positivity are used (the finding of a predominant organism or more than 10 gram-positive, lancet-shaped diplococci per oil immersion field [×1000], or both), the specificity of the Gram stain for identifying pneumococci has been shown to be 85%, with a sensitivity of 62%.[94] Because pneumococci may be part of the nasopharyngeal microbiota in 10% to 50% of healthy adults and often colonize the lower airways in patients with chronic bronchitis, identification of the organism does not mean that it is the cause of disease.[95] However, it is our experience that the large number of pneumococci necessary to produce a positive Gram stain is unusual in carriers.

Microscopic sputum examination can be helpful to identify organisms other than pneumococci. The finding of small gram-negative coccobacillary organisms on sputum Gram stain is characteristic of *H. influenzae* (see Fig. 69-4). However, the sensitivity of the sputum Gram stain for detecting *H. influenzae* is usually less than that for *S. pneumoniae* and has been reported to be 40% to 80%. Staphylococci appear as gram-positive cocci in tetrads and grapelike clusters (see Fig. 69-5). Organisms of mixed morphology are characteristic of anaerobic infection. Few bacteria are seen with legionnaires' disease, *Mycoplasma* pneumonia, and viral pneumonia. Examination of induced sputum obtained after patients undergo nebulizer treatment with 3% saline solution has been a useful means of diagnosing *Pneumocystis* pneumonia in patients with AIDS. The use of commercially available monoclonal antibodies or Giemsa's, Gomori's methenamine

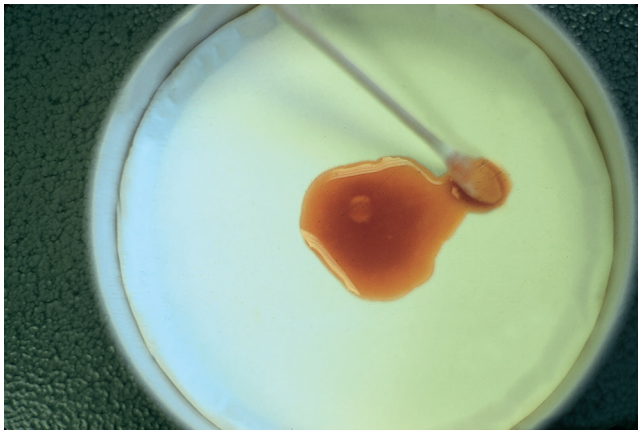

FIGURE 69-1 **"Currant-jelly" sputum associated with *Klebsiella pneumoniae* pneumonia.**

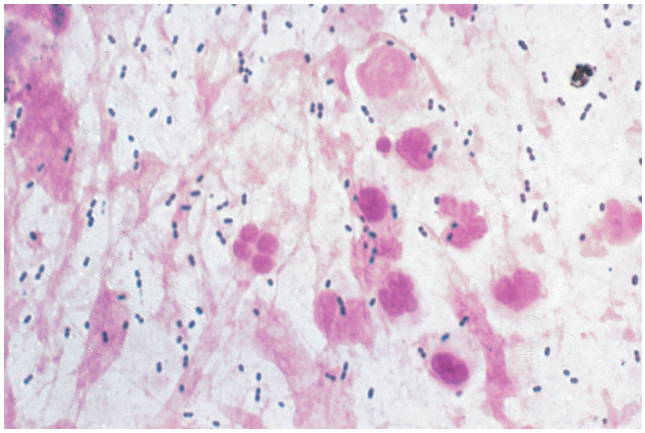

FIGURE 69-2 **Expectorated sputum with gram-positive, lancet-shaped diplococci from a patient with pneumococcal pneumonia.**

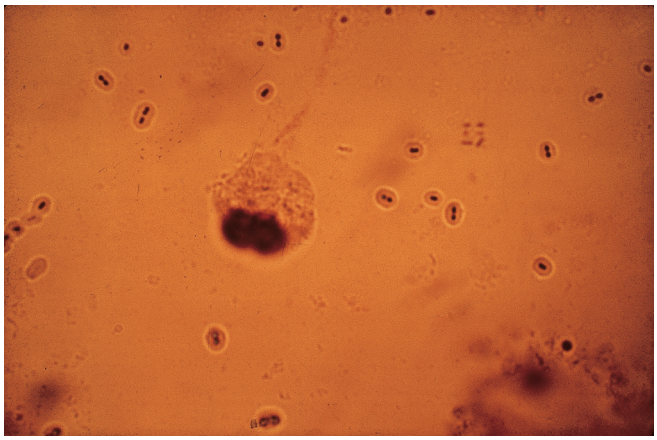

FIGURE 69-3 **Expectorated sputum demonstrating a positive quellung reaction in a patient with pneumococcal pneumonia.**

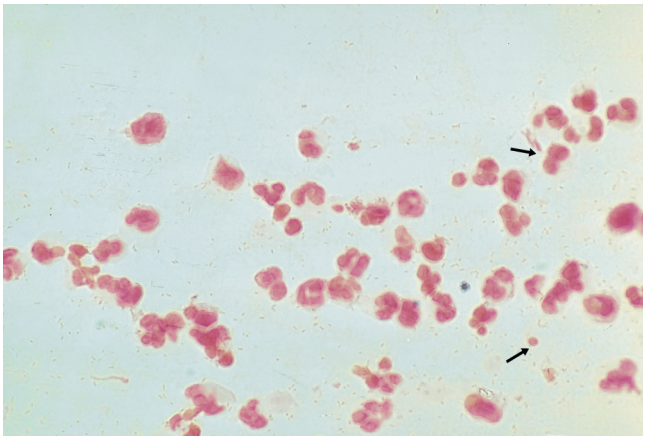

FIGURE 69-4 Expectorated sputum with gram-negative coccobacillary forms *(arrows)* from a patient with *Haemophilus influenzae* pneumonia.

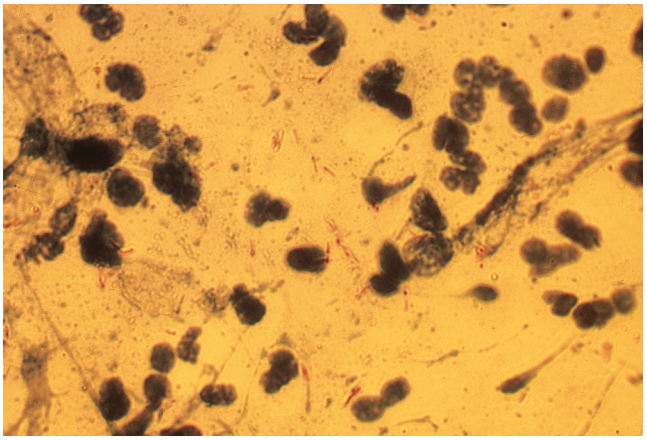

FIGURE 69-7 Expectorated sputum with acid-fast bacilli in a patient infected with *Mycobacterium tuberculosis.*

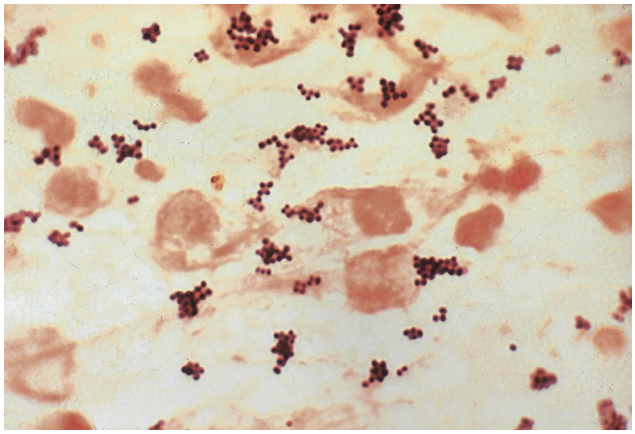

FIGURE 69-5 Expectorated sputum with clusters of gram-positive cocci in a patient with *Staphylococcus aureus* pneumonia.

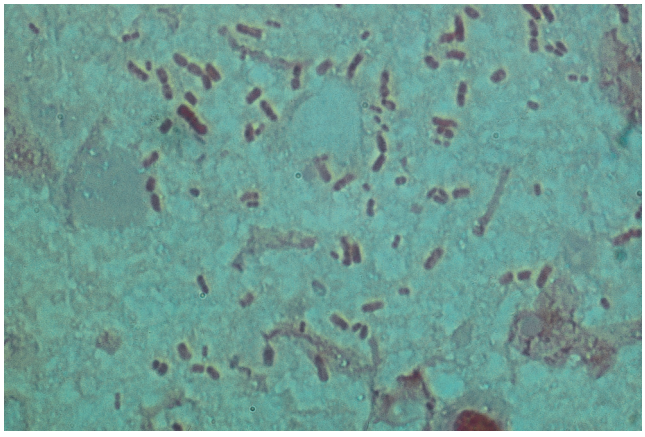

FIGURE 69-6 Expectorated sputum with gram-negative rods in a patient with *Klebsiella pneumoniae* pneumonia.

silver, or toluidine blue O stains has led to a diagnosis in up to 50% of cases, making more aggressive diagnostic procedures unnecessary. Special sputum staining techniques are important in identifying other organisms such as mycobacteria (Fig. 69-7).

Sputum culture as a means of diagnosing pneumonia is as controversial as the sputum Gram stain. Not all patients with pneumonia will produce sputum. Even when they do, studies of patients with bacteremic pneumococcal pneumonia have found sputum culture positivity rates varying between 29% and 94%.[87] Similarly, only 35% to 73% of sputum cultures are positive with proven *H. influenzae* pneumonia.[96,97] Both *S. pneumoniae* and *H. influenzae* are relatively fastidious and the sensitivity of cultures decreases with the prior use of antibiotics or with delays in transport of specimens to the clinical microbiology laboratory. Beyond these concerns with test sensitivity, sputum cultures have frequently been shown to yield more bacterial species than more invasive methods of obtaining respiratory tract secretions.[98] A lack of correlation between findings from sputum culture and findings from blood cultures and serologic studies has been observed.

Several key parameters have been identified in efforts to maximize the diagnostic yield from sputum culture. Procurement of adequate sputum samples is an essential first step. With increasing numbers of epithelial cells and decreasing numbers of neutrophils, an increased amount of oropharyngeal contamination is present, as indicated by the isolation of more bacterial species. The presence of alveolar macrophages does not alter the bacteriologic findings when substantial numbers of epithelial cells are present, indicating that otherwise adequate samples of sputum can be contaminated with oropharyngeal contents and thereby rendered nondiagnostic. This type of initial screening has proved helpful in differentiating adequate sputum samples from saliva, thereby increasing the diagnostic yield of sputum culture.

When culture of sputum is delayed, the isolation of pneumococci is less likely because of overgrowth by oropharyngeal microbiota. Rapid processing of samples is therefore another important factor leading to higher diagnostic yield. Some reports suggest that with adequate sputum samples and prompt culture of specimens, the diagnostic yield of the sputum culture may be improved.[87]

Antigen detection in respiratory secretions has been used for more than 2 decades to try to maximize the diagnostic yield of sputum, especially for infections caused by *S. pneumoniae, Pneumocystis, Legionella pneumophila,* and a variety of respiratory viruses. The direct fluorescent antibody assays for *L. pneumophila* and *Pneumocystis jirovecii* are the most commonly utilized, with sensitivities of 25% to 75% for *Legionella* and 80% for *Pneumocystis.*[99,100] The sensitivity for *Pneumocystis* may be less for patients with causes of immunosuppression other than HIV disease.[101] Specificities of approximately 90% have been reported in the assays for each pathogen. Non-*pneumophila* and *pneumophila* non–serogroup 1 strains of *Legionella* may be missed in these assays, and the test needs to be performed by experienced technologists. For other organisms such as *Chlamydia,* problems with colonization versus infection, varying sensitivities, and cross-reactivity with nonpathogens have limited the usefulness of the study.

Detection of microbial nucleic acid in respiratory tract secretions, both nasopharyngeal and sputum, remains an area of ongoing study.[102-104] Nucleic acid amplification assays, especially polymerase chain reaction (PCR) are particularly attractive because they have the capability of detecting minute amounts of material from potential pathogens, do not appear to be greatly influenced by prior antibiotic therapy, and can be performed quickly. Whereas a variety of PCR techniques have been

described, U.S. Food and Drug Administration (FDA)-licensed assays exist for only *M. tuberculosis, Legionella* spp., and respiratory viruses. Assays for more commonly encountered organisms such as *S. pneumoniae, H. influenzae, Mycoplasma,* and *Chlamydia* spp. have been developed, but lack of standardization and difficulty in determining true infection from colonization remain problematic. False-negative results have been reported because of the presence of natural inhibitors. Although the PCR assay has been used to detect *P. jirovecii,* published studies have detected positive results in the setting of negative cultures and absence of clinical features of infection. PCR techniques have been used to identify DNA from *M. tuberculosis* in both sputum and lavage fluid. Sensitivities of 90% to 100% have been seen with patients who are acid-fast bacilli (AFB) smear positive, and results are reported as 50% to 70% in patients who are AFB smear negative; specificities as high as 99% have been noted. However, PCR assay may remain persistently positive in patients recently treated for tuberculosis and with no apparent active disease. Several individual pathogen and multiplex real-time PCR assay systems have become commercially available for the detection of community respiratory viruses.[103] The test systems differ for viral pathogens that they detect, and "in-house" assays for select pathogens are frequently not FDA approved. Available assays can detect influenza A, influenza B, parainfluenza viruses, respiratory syncytial virus (RSV), human metapneumovirus, coronaviruses, rhinoviruses, and bocavirus in respiratory secretions with high sensitivity and specificity for the presence of viral nucleic acid. However, it is unclear if positive results indicate upper rather than lower respiratory tract infection, colonization, or true infection of the lung or even the presence of infectious virus particles. Overall, these molecular assays have clear utility for research purposes.[61,83] However, they remain expensive, and although they may be of benefit in the management of severely ill hospitalized patients and in select clinical settings, the cost-effectiveness for the general management of acute pneumonia has not yet been defined.

Fiberoptic Bronchoscopy

Although the sputum examination should always be included in the initial evaluation of patients with pneumonia, it may be inadequate for a presumptive diagnosis, particularly in the immunocompromised host or the patient on mechanical ventilation in whom there is a broader range of potential pathogens. Fiberoptic bronchoscopy allows for the collection of lower respiratory tract cultures through the use of protected brush catheters and the performance of either or both bronchoalveolar lavage (BAL) and transbronchial biopsy.[105] BAL, in which a segment of the lung is washed with sterile fluid, samples approximately 100 million alveoli and consequently examines a larger segment of the lung than either the protected specimen brush or a transbronchial biopsy.

The use of the protected brush catheter and quantitative culturing of material obtained from the procedure have both minimized the problem of oropharyngeal contamination and helped to differentiate colonization from true infection. Approximately 10^6 to 10^8 organisms per milliliter are present in lung tissue involved with pneumonia. Accounting for dilution of samples, a bacterial count of more than 10^3 to 10^4 has been used as a breakpoint for determining the clinical significance of an isolate. When studied prospectively early in the course of CAP, bronchoscopy has yielded a diagnosis in approximately 50% of patients.[106]

Bronchoscopy with a protected specimen brush has been shown to have sensitivities as high as 82% to 100% and as low as 36% with specificities as high as 60% to 77% and as low as 50% for the diagnosis of bacterial pneumonia.[107-109] Differences in exclusion and inclusion criteria, different definitions of pneumonia, and the acceptance or rejection of patients with recent antibiotic changes may explain the different results.[110] The use of antibiotics markedly diminishes the diagnostic yield of the procedure. Most bacterial species initially found by a protected specimen brush are undetectable after 72 hours of antibiotic therapy, and the majority of organisms found are resistant to the antibiotics given. These may have no role in the infection. However, in a patient with ongoing pneumonia despite antibiotic therapy, bronchoscopy with a protected specimen brush should pick up resistant organisms that may be playing a role in infection.[107] BAL has also been used for the diagnosis of atypical pneumonias, including those caused by *Legionella* species and *M. pneumoniae.*

False-negative findings are seen in up to 30% to 40% of patients, which may reflect the fact that bacterial counts may differ by 50-fold in areas of infected lung versus noninfected adjacent areas, making the sampling site an important consideration. Other possible explanations include prior antibiotic use, technique problems, and, in some cases, an early stage of pneumonia in which bacterial numbers are not yet high enough to reach the breakpoint of the procedure.

Bronchoscopy with BAL has been particularly valued for the immunocompromised host, including patients with AIDS. In patients with AIDS, diagnostic yields for *Pneumocystis* pneumonia of 89% to 98% have been reported.[111] Excellent yields have also been noted in detecting cytomegalovirus in patients with AIDS, as well as in bone marrow and solid-organ transplant recipients, although detection of this agent alone does not prove it as the cause of pneumonia.[112] The high degree of immunosuppression in these patient populations permits high levels of the pathogens to flourish, which makes their detection easier.

BAL has also been shown to be useful for diagnosis of pulmonary *M. tuberculosis* and fungal infections. Culture of BAL material has a sensitivity of approximately 85% for *M. tuberculosis,* even in the setting of negative culture of expectorated sputum and gastric aspirate samples.[113] With the use of strict diagnostic definitions, performance of PCR and galactomannan assays on BAL has approximate sensitivities and specificities of 77% and 93% for invasive pulmonary aspergillosis.[114] Bronchoscopy with calcofluor staining and fungal culture can also be helpful in the diagnosis of pulmonary histoplasmosis, cryptococcosis, and coccidioidomycosis.[105,115,116]

Both bronchoscopy and BAL have been used widely in patients with ventilator-associated pneumonia (VAP).[117] The "bacteriologic strategy" recommended in the IDSA/ATS guideline on VAP recommended bronchoscopy, BAL, or endobronchial aspiration to establish the presence or absence of pulmonary infection as well as to determine the specific etiology.[77] A prospective multicenter trial found that the use of bronchoscopy with BAL and quantitative culture did not improve clinical outcomes as compared with nonquantitative culture of endotracheal secretions.[118]

Bronchoscopy is not without risk. It can induce respiratory failure and the need for mechanical ventilation in hypoxemic patients. There is a risk for bleeding with both the use of protected brush catheters and transbronchial biopsies, as well as a lesser risk for pneumothorax. In patients with gram-negative pneumonia, a sepsis-like picture with increased temperature and decreased mean arterial pressure may follow the procedure. It should not usually be considered in patients with CAP unless the infection is severe or unresolving or a clear failure of antibiotic therapy is encountered, suggesting an occult process such as a concern of a minor obstructing lesion or a foreign body not seen on diagnostic imaging.[105]

Other Techniques

A variety of less invasive techniques have been used in attempts to determine the cause of pneumonia without resorting to bronchoscopy. Blind endotracheal suctioning with quantitative cultures has compared favorably with bronchoscopic procedures in investigation of VAP in some studies.[119] With a threshold of greater than 10^5 colony-forming units (CFU)/mL, the sensitivity for predicting VAP was comparable to that of lavage or protected brush procedures, although the specificity was somewhat lower.[119] Furthermore, no differences in mortality, length of ICU stay, or duration of mechanical ventilation were noted when quantitative endotracheal cultures were used as the sole means of diagnosis compared with BAL and protected specimen brushing. Others have reported false-negative rates of over 30% and many more organisms isolated by endotracheal suctioning than by brushing.[120] In addition, in the setting of VAP, concern remains about sampling error, as well as the potential for differing pathogens in different lung segments. At present, none of these techniques has been shown to increase the accuracy in diagnosing VAP, and studies of clinical outcome have found that mortality from VAP is unchanged independent of whether bronchoscopic or nonbronchoscopic procedures are used for diagnosis.[121,122]

Lung Biopsy

Direct means of obtaining diagnostic material in patients with pneumonia include percutaneous lung aspiration, transbronchial lung biopsy, video-assisted thoracoscopy, and open lung biopsy. These procedures are usually reserved for cases of severe pneumonia in impaired hosts and in pediatric populations, in whom sputum is not routinely available.

Biopsy procedures are rarely indicated in the previously well patient with acute pneumonia. The indications and usefulness of these invasive procedures remain controversial. Blind lung aspiration has provided a diagnostic yield of 30% to 82% in adults and children with diffuse lung infiltrates, although false-negative rates of up to 18% have been reported.[98,123,124] Computed tomographic (CT)-guided percutaneous lung aspiration has been shown to be effective in diagnosing focal fungal infections in the transplant population.[125] Bleeding and pneumothorax have been reported as major complications in 5% to 39% of procedures.[123]

Open lung biopsy remains the definitive invasive procedure for making an etiologic diagnosis of pneumonia in immunosuppressed patients, with diagnostic yields of 60% to 100%.[126,127] In immunocompromised patients, the incidence of unexpected diagnoses that can lead to a change in treatment can be over 50%, although the clinical utility seems significantly lower in the immunocompetent population.[127] The incidence of pneumothorax and bleeding is usually less than 10%, even in patients who are thrombocytopenic.[126]

Examination of Pleural Effusions

The characteristics of pleural effusions and their importance in the differential diagnosis of pulmonary disease are discussed in Chapter 70. Pleural effusion or parapneumonic effusion will occur in 20% to 40% of hospitalized patients with pneumonia, and the incidence of severe pleural involvement has been increasing in recent years.[128-130] The incidence of pleural effusions associated with pneumonia varies with the etiologic agent, from 40% to 57% with pneumococci, to 50% to 70% with gram-negative bacilli, and up to 95% with β-hemolytic streptococci.[91,131] Pleural fluid cultures, when positive, are specific for the organism causing the underlying pneumonia. Furthermore, analysis of pleural fluid may play a major role in determining when drainage is necessary as well as differentiating other causes of pulmonary infiltrates that may mimic bacterial pneumonia, including tuberculosis, tumors, pulmonary emboli, and collagen vascular diseases. If neutrophils are not the predominant cell type seen in the pleural space, a diagnosis other than bacterial pneumonia should be sought. Pleural biopsy specimens from patients with acute bacterial pneumonia are nonspecific and are therefore of little use in the differential diagnosis.

Parapneumonic effusions can be divided into three stages.[128,131] The first stage or exudative stage is culture negative, has a pH of greater than 7.2, glucose level greater than 60 mg/dL, and a lactate dehydrogenase level that is less than three times the upper limit of normal. This stage is due to pulmonary interstitial fluid entering the pleural space and increased permeability of the capillaries in the pleura. These uncomplicated pleural effusions usually resolve with therapy for the underlying disease. Without appropriate therapy, pleural effusions become infected with the organisms causing the underlying pneumonia and develop into the second stage or fibropurulent stage. This stage is associated with positive microbial cultures, pH less than 7.2, glucose level less than 60 mg/dL, and lactate dehydrogenase level that is greater than three times the upper limit of normal. Such complicated pleural effusions require drainage. The most sensitive finding in determining if a pleural effusion needs drainage is a pleural fluid pH less than 7.2. This usually occurs before the other chemical parameters associated with complicated pleural effusions develop.[128] If pH is used to determine if an effusion is to be drained, it must be measured with a blood gas machine, not a pH meter or pH indicator strip, which can be inaccurate. If left untreated, fibropurulent pleural effusions will develop into stage three effusions in which a thick pleural rind is formed that restricts normal lung expansion.

Empyema is defined as pus in the pleural space and represents a late manifestation of complicated pleural effusions. The presence of empyema mandates draining the pleural space.

Complicated pleural effusions can have a positive culture result in up to 24% of cases, making thoracentesis and culture of fluid a valuable means of making an etiologic diagnosis of the underlying pneumonia.[132,133] Other diagnostic tools have proven useful in identifying organisms associated with pleural effusions. PCR technology can be useful in detecting *M. tuberculosis* as well as defining the etiology in culture-negative cases.[133,134] Adenosine deaminase, an enzyme associated with lymphocytes, may also be used to detect *M. tuberculosis,* with both sensitivity and specificity of over 90%.[135,136]

Blood Culture, Serologic Studies, and Urine Studies, Including Antigen Detection

Blood cultures are positive in between 4% and 17% of patients hospitalized with CAP, with the frequency of positive results increasing with the severity of illness.[83,106,137-139] Recent studies have suggested that positive blood cultures add little to the management of patients hospitalized with CAP and are not predictive of increased mortality.[140-142] However, the presence of true-positive blood cultures is highly specific, may be helpful in narrowing antibiotic use, and may identify the presence of unusual organisms that would not be adequately covered by routine empirical antibiotic coverage.[143,144] Recent work has shown that several clinical features can be used to predict patients with a higher likelihood of having bacteremia.[138,139] In particular, patients who have two or more of the findings of chronic liver disease, pleuritic pain, tachycardia, tachypnea, or systolic hypotension and the absence of prior antibiotic therapy have at least a 14% incidence of bacteremia, with a bacteremia incidence of up to 63% in those with four or more of these findings.[139] It is clear that blood cultures should be obtained before antibiotic administration in all patients with CAP ill enough to be hospitalized who have two or more of these features, as well as in those patients who are immunocompromised, those being admitted with HCAP, or those who acquire pneumonia in the hospital. The IDSA and ATS have also recommended blood cultures for patients being admitted to an ICU or who have a cavitary lesion, leukopenia, active alcohol abuse, asplenia, a positive pneumococcal urinary antigen, or a pleural effusion.[84] Furthermore, because the etiology of pneumonia is not always determined, assessment of clinical response to initial therapy is important, and blood cultures should be obtained in patients not responding to antibiotic therapy.[144]

A variety of assays have been utilized to detect pathogens that have been difficult to isolate using routine culture techniques. Serologic assays have been used to diagnose infections caused by *Legionella* spp., *M. pneumoniae, Chlamydia* spp., and *Coxiella burnetii.* The sensitivity and specificity of the assays vary, and their overall usefulness in making a rapid diagnosis is limited. The Centers for Disease Control and Prevention (CDC) and the Laboratory Centre for Disease Control (LCDC) have established diagnostic standards for *Chlamydia* assays.[145] Microimmunofluorescence (MIF) for serum chlamydial antigens has been recommended, although enzyme immunoassays are also available and may be more sensitive and specific.[146] For the MIF assay, an IgM titer of greater than 1:16 or a fourfold rise in IgG value is used to define positivity. Use of a single IgG value is not viewed as a definitive test. Because the present assays show day-to-day variation, it has been suggested that acute and convalescent titers be assayed at the same time. A fourfold rise in IgG rather than a single clinical titer is accepted as a positive test for *M. pneumoniae.*[147] Although an elevated IgM titer suggests a recent infection, reinfection with *Mycoplasma* occurs frequently and a rise of IgM may not always be seen.[148] Cold agglutinins may be elevated in infections with *M. pneumoniae.* Titers greater than or equal to 1:4 are suggestive of *M. pneumoniae* infection. For both mycoplasmal and chlamydial infections, nucleic amplification technologies are being examined as alternative diagnostic modalities.[145,147,149]

S. pneumoniae produces a variety of antigens and surface markers that are type or species specific.[150] Although both antigen and antibody detection methods in serum have been studied, none has become clinically significant. PCR techniques have been applied to whole blood for the detection of pneumococci, but the assays remain experimental.[151]

Serum assays for cryptococcal capsular antigen have relatively low sensitivity for cryptococcal pneumonia but are highly specific and of benefit in the management of immunocompromised patients as well

as immunocompetent individuals suspected of infection with *Cryptococcus gatti*.[152] Serum assays for (1→3)-β-D-glucan, a component of the cell wall of fungi except for *Cryptococcus* spp. and Zygomycetes, have high specificity for invasive fungal infections and can be used for detection of invasive pulmonary aspergillosis in immunocompromised hosts, as well as for the detection of pneumonia due to the endemic fungi *Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis* in patients with appropriate geographic exposure.[153,154,155] In addition, β-D-glucan is also a component of the cell wall of *P. jirovecii,* and serum assays have a sensitivity of over 95% and specificity over 80% for *Pneumocystis* pneumonia in both HIV-positive and HIV-negative immunocompromised patients.[154,156]

A variety of cytokines are released into the circulation as a result of infection.[157-160] Evidence suggests that these biomarkers may be useful adjuncts in diagnosing pneumonia and predicting severity of disease.[157-160] The calcitonin family of gene products, especially procalcitonin, C-reactive protein, and soluble triggering receptor expressed on myeloid cells (STREP-1), have been the markers most often associated with pneumonia. Procalcitonin appears to be the earliest marker to appear during the course of infection. Clinical trials have now found that the presence of an elevated procalcitonin level (>0.25 to 0.5 μg/L) can be used to identify patients requiring treatment for pneumonia and, based on whether levels fall, how long antibiotics should be continued without increasing the risk for an adverse outcome.[161-163] Procalcitonin has also been used as a gauge of pneumonia-related mortality.[164] C-reactive protein is an acute-phase reactant produced in the liver as a response to a variety of stimuli, including infection. Normal values of less than 10 mg/L are unusual in patients with pneumonia and can be used to exclude the diagnosis. Levels of 100 mg/L or greater suggest the diagnosis of pneumonia and have been associated with an increased 30-day mortality and a greater likelihood of need for ventilator or vasopressor support (i.e., severe pneumonia).[160] In comparative trials, C-reactive protein appears to have a better ability to define infection and procalcitonin the clinical severity, although definitive studies are lacking.[159] Other cytokines studied include IL-6 and TNF-α, but their correlations with pneumonia appear less consistent. Cortisol levels have also been shown to predict the severity of pneumonia and the chance of survival.[165,166] Although the clinical trials with procalcitonin have shown a reduction in antibiotic costs, there can be significant expense in performing these biomarker assays, and large-scale randomized studies of their cost-effectiveness are lacking. Thus, their role in diagnosis and severity assessment in pneumonia has not been clearly defined.

Antigen detection in urine rather than blood or sputum has become a successful means of detecting some important pulmonary pathogens. Soluble *L. pneumophila* antigen can be detected in urine using a commercially available enzyme immunoassay. Although it is useful only for detecting *L. pneumophila* serogroup 1, this assay offers the advantage of being rapid and noninvasive and has a sensitivity of 80% to 95% and a specificity estimated to be 99%.[99] An additional relative limitation of this assay is that antigenuria may persist for weeks to months after therapy.

An immunochromatographic membrane test has been developed to detect the C polysaccharide cell wall antigen found in all *S. pneumoniae* in urine of patients with pneumonia (Binax NOW).[167] This has been reported to be an extremely useful means of diagnosing pneumococcal pneumonia. Using a variety of standard diagnostic tests as controls, overall sensitivities of 65.5% to 100%, specificities of 94% to 100%, and positive predictive values of 62% have been noted.[168-170] Sensitivities have, in general, been high in bacteremia episodes, with the yields increased slightly by concentrating the urine. The test is not affected by the prior use of antibiotics. Potential problems with the urinary antigen assay include weakly positive results caused by nonpneumococcal organisms, false-positive results in children with nasopharyngeal carriage rather than true infection, and positive results lasting for weeks after the infection has resolved.[169,171] Shortfalls of the test are that no organism is isolated and no antibiotic susceptibilities can be carried out. In addition, retrospective analysis has not found an impact of the routine use of the test on antibiotic prescribing practices for patients with suspected pneumonia, suggesting that its use be reserved for research purposes or situations such as unresolving or worsening infection in which defining the precise cause of pneumonia is clinically important.[172]

Radiologic Examination

Chest radiography plays a critical role in the diagnosis of pneumonia, and for many it represents the gold standard of making a clinical diagnosis. The differential diagnosis of respiratory complaints and abnormal physical findings includes upper and lower respiratory tract infection as well as an array of noninfectious entities. Demonstration of an abnormal chest radiograph with pulmonary infiltrates consistent with pneumonia differentiates a patient population that may benefit from antibiotic therapy from the populations that will not. Because overuse of antibiotics for therapy for upper respiratory tract infections has been documented and may contribute to the growing problem of antibiotic resistance, identifying patients who really should be receiving antibiotic therapy is clearly of importance. The chest radiograph is readily available, is reasonably reliable (despite interobserver variability), and should be obtained in most patients suspected of having pneumonia.[84,173,174] The extent and nature of radiographic abnormalities may define patients who are more seriously ill and may need close monitoring.

The patterns of infiltrates found on chest radiographs in patients with pneumonia usually are not helpful in making a specific etiologic diagnosis (Fig. 69-8A and B).[174] However, certain features may be of some diagnostic aid. Lobar consolidation, cavitation, and large pleural effusions support a bacterial cause (Figs. 69-9 and 69-10). Most lobar pneumonias are pneumococcal, although pneumococcal pneumonias are not necessarily lobar. When bilateral diffuse involvement is noted, *Pneumocystis* pneumonia, *Legionella* pneumonia, or a primary viral pneumonia should be suspected. Staphylococcal pneumonia may result from infection metastasizing from a primary focus unrelated to the lung. In these cases, multiple nodular infiltrates throughout the lung may be seen. Staphylococci may cause marked necrosis of lung tissue with ill-defined thin-walled cavities (pneumatoceles), bronchopleural fistulas, and empyema, especially in children (Fig. 69-11). *S. aureus* producing the Panton-Valentine leukocidin, whether methicillin resistant or not, is associated with necrotizing pneumonia with multilobar cavitary lesions and is frequently associated with pleural effusions and empyema.[175,176] Although pneumatoceles are diagnostically significant findings in staphylococcal pneumonia, they may be seen in pneumonias with other causes, including *K. pneumoniae, H. influenzae, S. pneumoniae,* and, more rarely, *Pneumocystis.* Pulmonary infections due to *Pseudomonas* may cavitate. *Pseudomonas* and other gram-negative bacilli most commonly cause lower lobe pneumonia.

Aspiration pneumonia should be considered along with gram-negative and staphylococcal pneumonias as a source of necrotizing pneumonia, cavitation, and empyema. Aspiration pneumonia commonly involves either the superior segment or the basilar segment of either lower lobe or the posterior segment of the upper lobes, depending on whether aspiration occurred in the dependent or the upright position. Chronic aspiration most commonly results in bilateral lower lobe pneumonia, although it may involve one side more than the other.

Viral infection of the lower airway involves respiratory epithelium and parenchyma adjacent to terminal respiratory bronchioles. Diffuse hemorrhagic congestion of alveolar septa may occur as well.[177] The radiographic concomitants of these pathologic findings usually involve patchy areas of peribronchial ground-glass opacity, airspace consolidation, and poorly defined small nodules. Diffuse and localized involvement with both interstitial and alveolar patterns has been noted (Fig. 69-12).[177] There is little radiologic distinction between the various viral causes of pneumonia. Influenza pneumonia is associated with poorly defined, patchy airspace consolidation with rapid confluence. Varicella pneumonia usually involves peribronchial involvement with nodular infiltrates. Adenovirus, herpes simplex virus, and cytomegalovirus, all of which are more common in immunocompromised hosts, may be associated with diffuse bilateral bronchopneumonia, areas of overinflation, atelectasis, and nodular opacities. Lobar or subsegmental consolidation mimicking bacterial pneumonia may also be seen in patients infected with adenovirus and herpes simplex virus. Hantavirus pneumonia usually presents as interstitial edema, which may progress to consolidation representing a pulmonary capillary leak syndrome.

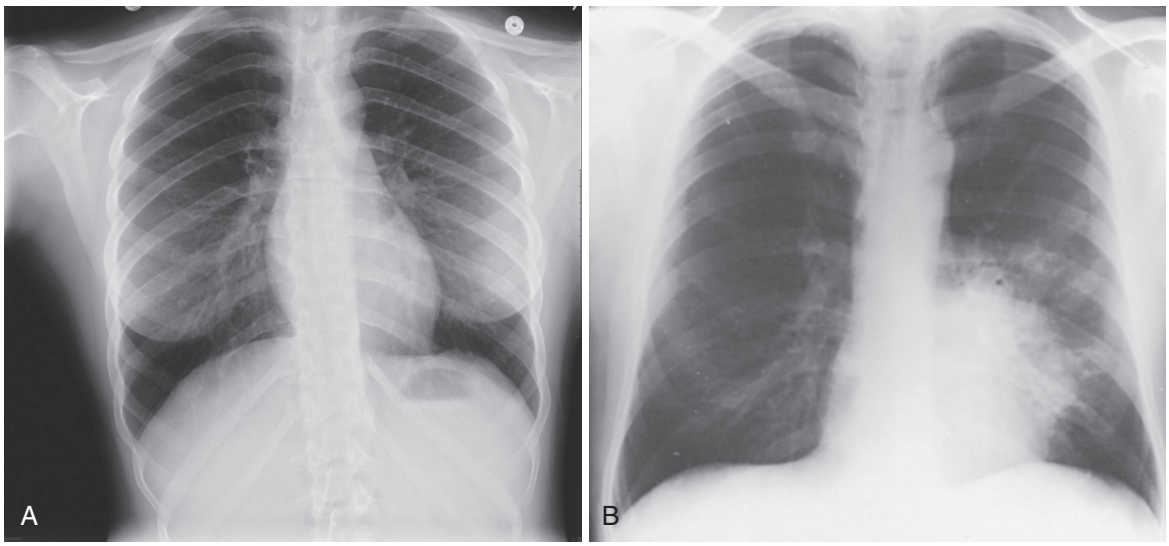

FIGURE 69-8 **A,** Normal chest radiograph. **B,** Patchy infiltrate representing bronchopneumonia in a patient with *Streptococcus pneumoniae* infection.

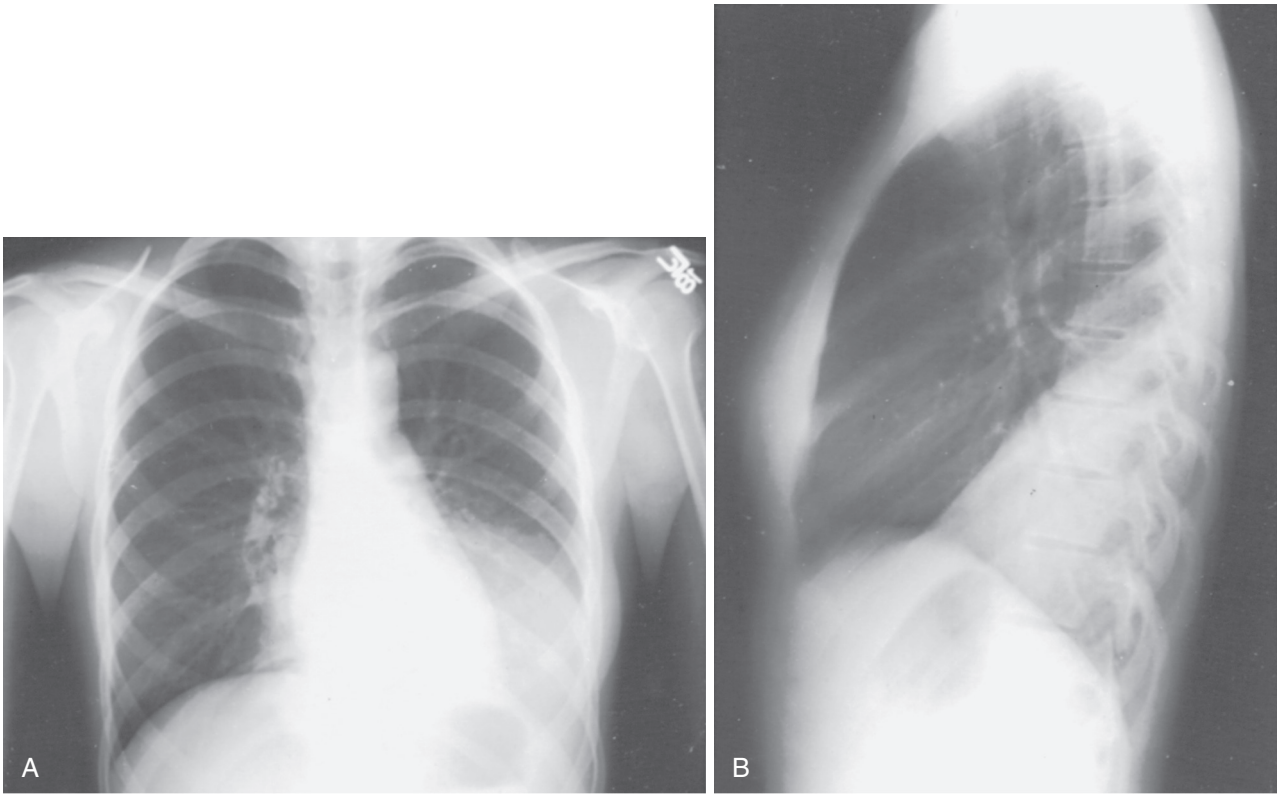

FIGURE 69-9 **A,** Chest radiograph showing dense left lower consolidation consistent with bacterial pneumonia, in this case caused by *Streptococcus pneumoniae.* **B,** Lateral radiograph of a patient with left lower lobe pneumococcal pneumonia.

Bilateral involvement and pleural effusion are common and when present are associated with a worse clinical outcome.[178] Both the severe acute respiratory syndrome (SARS) coronavirus and a newer novel coronavirus identified in 2012 can cause pneumonia that begins predominantly with bilateral interstitial basilar infiltrates and progresses to severe symmetrical airspace disease.[179-181] Other recently defined viral pulmonary pathogens are the human metapneumovirus and bocavirus. Most cases of human metapneumovirus infection involve upper respiratory tract infections in children; pneumonia in adults has been described.[182,183] Multilobar infiltrates have been noted in 50% of cases, and pleural effusions are not uncommon. Bocavirus pneumonia is more frequently reported in children and has been associated with patchy or interstitial infiltrates that are similar to those found with other common respiratory virus infections.[184]

Mycoplasmal pneumonia often manifests as an interstitial pattern in a peribronchial and perivascular distribution.[185] Consolidation is noted in approximately 38% of patients, usually in the lower lobe. Once this consolidation stage is reached, radiologic differentiation between bacterial and mycoplasmal pneumonia is difficult. Cavitation is rare, although pleural effusions may be seen in approximately 20% of cases.[185,186] *Chlamydia pneumoniae* predominantly causes unilobar disease associated with air bronchograms.[174]

Legionnaires' disease may initially present as a radiographic picture similar to that of mycoplasmal pneumonia. A patchy interstitial or

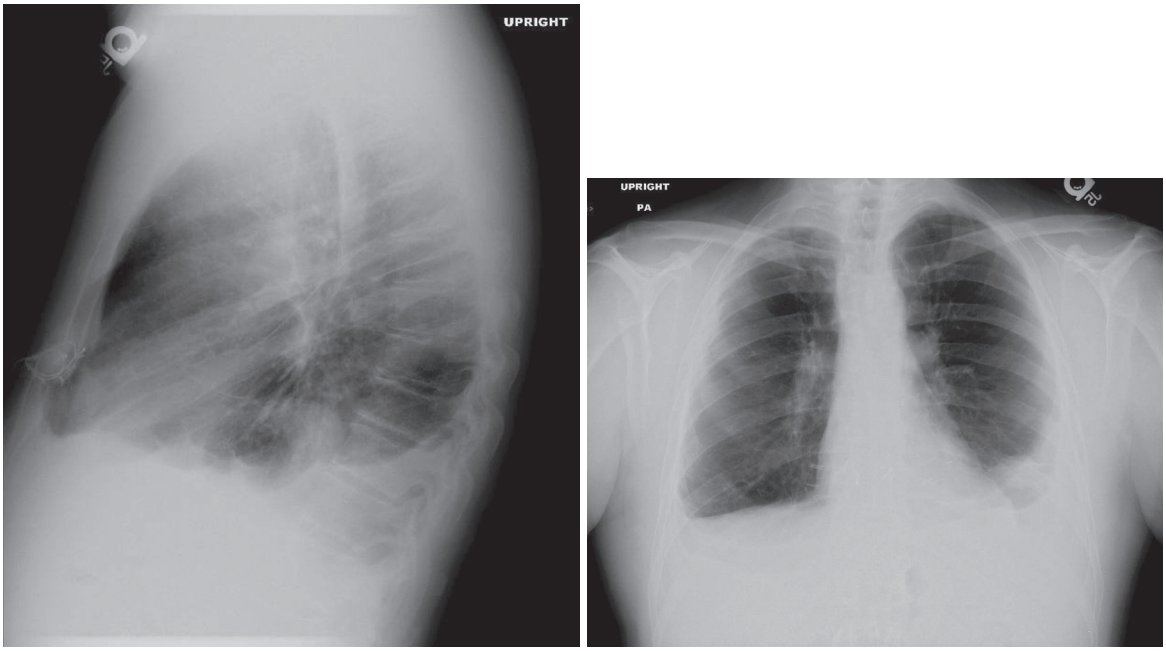

FIGURE 69-10 Chest radiographs showing a large left pleural effusion in a patient with *Klebsiella pneumoniae* pneumonia.

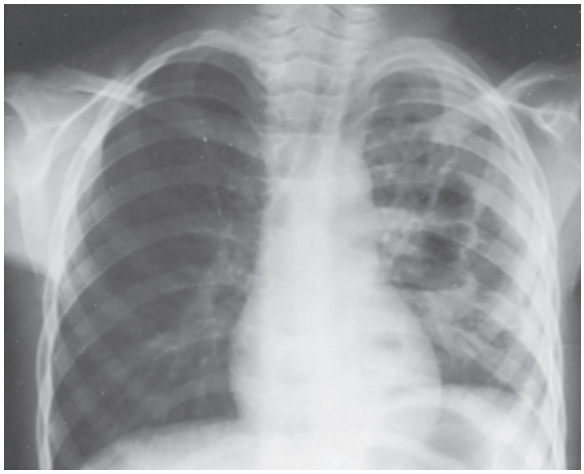

FIGURE 69-11 Pneumatocele formation in the left upper lobe of a patient with staphylococcal pneumonia.

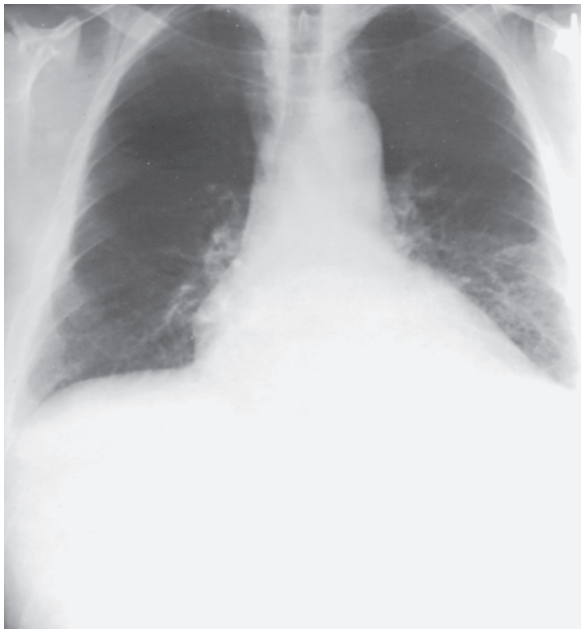

FIGURE 69-12 Bilateral involvement with a mixed interstitial-alveolar pattern in a patient with viral pneumonia.

finely nodular pattern is seen in the lower lobe.[187] However, unlike the situation with mycoplasmal pneumonia, pneumonia with more than two-lobe involvement is commonly seen. Rapid progression and pleural effusions are also common. Pneumonia caused by *Legionella micdadei* may present as pulmonary nodules, either single or multiple, as well as segmental infiltrates. As in pneumonia caused by *L. pneumophila,* rapid radiologic progression of the disease is characteristic.[188]

High-resolution CT has been shown to improve radiographic characterization of lung infection.[189-191] In the immunocompetent host, chest CT is most helpful in evaluating recurrent pneumonia or infections unresponsive to therapy. Pneumonia developing behind an obstruction caused by tumors or other masses and lung abscess may also be better defined by CT than by routine chest radiographs.[189] Compared with a routine chest radiograph, high-resolution CT detects lung abnormalities more often and does a better job in defining disease in the upper and lower lobes and in the lingula. However, exposure to more radiation (the radiation from one CT scan equals that from six to seven chest radiographs) and the increased expense (approximately seven times the cost of a chest radiograph) has limited its use as the initial radiographic procedure. Furthermore, it is unclear if all abnormalities found on the chest CT scan truly represent pneumonia.[190] In the immunocompromised host in whom infection is only one of the possible causes of abnormal chest radiographs, chest CT or one of its variations, such as spiral CT or high-resolution CT, may aid in better defining a "questionable" chest radiograph and may be helpful in localizing involved areas of lung as a guide to biopsy procedures. CT scans are also more sensitive in defining parenchymal disease in the ICU setting. Certain infections, such as those caused by *Aspergillus, M. tuberculosis,* and *Pneumocystis,* have characteristic appearances on CT that in the correct clinical setting may make invasive procedures unnecessary. Both ultrasound and CT imaging may be more sensitive in defining pleural effusions than plain radiographs.[191] Techniques such as perfusion magnetic resonance imaging have been shown to be able to differentiate pneumonia from COPD and pulmonary emboli. The clinical utility of these techniques remains to be defined.

Nuclear medicine procedures have been used to detect pneumonia. These procedures include gallium-67 citrate scans, indium 111–labeled granulocyte scans, technetium-99m diethylenetriaminepentaacetic acid aerosol clearance, and ^{18}F-fluorodeoxyglucose positron emission tomography.[192] These procedures have been used in patients with AIDS to define the presence of lung infection in the absence of abnormal chest radiographs. In patients with AIDS, diffuse uptake of gallium is usually seen with *Pneumocystis* infection but may also be seen with infection caused by *Mycobacterium avium-intracellulare* complex, cytomegalovirus, and *Cryptococcus neoformans* and in patients with lymphoma. Localized uptake may be associated with bacterial disease. Focal uptake corresponding to lymph node areas has been associated with infection with *M. avium-intracellulare* complex and *M. tuberculosis* and with lymphoma.

PNEUMONIA SYNDROMES

Acute Community-Acquired Pneumonia

A long list of bacterial, fungal, viral, and protozoal agents may cause pneumonia. Because initial evaluation rarely results in a specific etiologic diagnosis, antibiotic therapy is usually begun empirically. Defining pneumonia syndromes on the basis of clinical, epidemiologic, radiographic, and laboratory parameters, with a limited number of organisms commonly associated with each syndrome, has helped the clinician to select rational empirical therapy for the most likely organisms involved. Many of the syndromes have overlapping signs and symptoms, which at times makes clear identification of a specific syndrome in an individual impossible.[193,194] Increases in numbers of patients living longer, more and varied comorbidities, the increasing use of biologic immunomodulators such as TNF inhibitors, and expanded contact with various aspects of the health care system have led to a wider array of presentations, etiologic agents, and strategies for empirical therapy. Newly described microbial agents are being recognized as potential causes of CAP. Subgrouping syndromes under the general description of CAP may be made based on patient age, severity of illness, comorbidities, need for hospitalization, and epidemiologic setting.

Patients with acute CAP are usually in their middle 50s to late 60s. Peak incidences of disease in general occurs in midwinter and early spring, although disease due to *Legionella* is more frequent in the summer.[195] Still, there is no "pneumonia season" and disease takes place throughout the year. Most patients (58% to 89%) have one or more chronic underlying diseases. Immunosuppression related to malignancy, neutropenia, the chronic use of corticosteroids or other myelosuppressive agents, or HIV infection is being increasingly observed.[194,196]

Classically, CAP presents as a sudden onset of a chill followed by fever, pleuritic chest pain, and cough that produces mucopurulent sputum. The signs, symptoms, and physical findings vary according to the age of the patient, therapy with antibiotics before presentation, and the severity of illness. Patients typically present after several days of symptoms.[197] Cough is noted in more than 80% to 90% of patients and is productive in over 60%.[197-200] Chest pain is present in 35% to 48% of cases, chills in 40% to 70%, and hemoptysis in approximately 15%.[197,198,200]

A variety of nonrespiratory symptoms are associated with pneumonia, including fatigue (91%), anorexia (71%), sweats (69%), and nausea (41%).[54] Both respiratory and nonrespiratory findings occur less frequently in older age groups.[54]

Physical examination reveals fever in 68% to 78% of patients but may be seen less commonly in older populations. Tachypnea (respiratory rate >24 to 30 breaths/min) is noted in 45% to 69% of patients and may be more frequently seen in older age groups.[54] Tachycardia (pulse rate >100 beats/min) is noted in 45%. Rales are noted in approximately 70% of patients, and signs of consolidation in 20%[197]; but no combination of physical findings has been found to be adequate to confirm a diagnosis of pneumonia.[53]

Most commonly, the white blood cell count is in the range of 15,000 to 35,000/mm^3 and the differential cell count reveals an increased number of juvenile forms. Leukopenia may be noted and is a poor prognostic sign.[84] The hematocrit and the red blood cell indices are usually normal.

Sputum is thick and purulent and may be rust colored. The sputum Gram stain reveals numerous neutrophils and bacteria, often with a single organism predominating. Chest films show areas of parenchymal involvement, usually with an alveolar-filling process. There is moderate hypoxemia due to ventilation-perfusion abnormalities. Even with rigorous laboratory evaluation and using definitions of *definite, probable,* and *possible* causes, a microbiologic diagnosis may be made in 40% to 75% of cases of CAP.[55,201,202]

In the past, 40% to 80% of cases of acute CAP were caused by *S. pneumoniae.*[88] Whereas the pneumococcus remains perhaps the most important cause of pneumonia, more recent published reports have indicated that its relative importance has diminished.[203] It has been defined as the cause of pneumonia in as few as 6% of ambulatory patients and only 55% of hospitalized patients.[201,202] It has been hypothesized that the apparent decreased incidence of pneumococcal pneumonia is related to recognition of newer pathogens and diminished use and performance of microbiologic studies.[88] However, through a herd immunity effect, the increasing use of pneumococcal vaccine in children appears to be reducing the incidence of pneumococcal disease in adults and children.[204,205] Severe pneumococcal infections, including pneumonia, have been associated with prior splenectomy due either to trauma or to staging for Hodgkin's disease, abnormal immunoglobulin responses (myeloma, lymphoma, HIV infection), and functional asplenia due to systemic lupus erythematosus or marrow transplant.[206,207]

An estimated 5% to 7% of cases of acute CAP appear to be caused by *H. influenzae.*[201-203] The true incidence of this organism is obscured by the difficulty of isolating it from sputum and identifying it in sputum that has been Gram stained and by the difficulty of distinguishing colonization from infection. The age of patients, presence of underlying disease, and presentation are similar to those of pneumococcal disease. Although the use of the *H. influenzae* conjugate vaccine has decreased the incidence of invasive disease caused by *H. influenzae* type b, there is a strikingly increased incidence of invasive disease including pneumonia caused by nontypeable strains. In one recent series, over 50% of isolates from patients with invasive *H. influenzae* diseases were nontypeable.[208]

S. aureus has accounted for 1% to 2% of acute CAP cases,[201-203] and takes on increased importance as a cause of pneumonia in older adults and in those with influenza.[56] Patients who develop postinfluenza pneumonia are usually younger and have less underlying disease than most other patients with CAP. Although it had been believed that bacterial pneumonia in the setting of influenza develops after clinical influenza, studies during the 2009 H1N1 pandemic indicate that bacterial coinfection most likely arises at the peak of viral replication, with patients presenting an average of 6 days after symptom onset.[56] An elevated white blood cell count with a shift to the left, physical signs of pulmonary consolidation, and radiographic evidence of focal parenchymal disease develop, and the sputum Gram stain is consistent with bacterial pneumonia.

S. aureus may also cause pneumonia hematogenously, producing multiple bilateral round lesions that will frequently cavitate. Although this presentation has been characteristically associated with right-sided endocarditis in injection drug users, it can also be seen in association with infections of intravascular catheters and with staphylococcal soft tissue infections.[209,210]

As noted previously, since the late 1990s there has been an increase in the incidence of pneumonia due to community-associated *S. aureus* strains.[57,176] Patients have been young, had few if any comorbidities, and usually presented after a flulike illness with high fevers, leukopenia, tachycardia, tachypnea, hemoptysis, and rapid evolution on radiography to multilobar disease. These cases appear to be associated with *S. aureus* strains carrying the Panton-Valentine leukocidin toxin, regardless of whether they are methicillin resistant.[211] The adult respiratory distress syndrome has been a frequent complication in such cases, and mortality rates of over 50% have occurred.[176]

Aerobic gram-negative bacteria, exclusive of *H. influenzae,* and mixed aerobic and anaerobic infections cause most of the remaining cases of acute CAP. Gram-negative rods may cause anywhere from 2% to 10% of pneumonia cases. *Klebsiella pneumoniae, P. aeruginosa,* and *Enterobacter* spp. are the most often isolated organisms.[201-203,212] Gram-negative bacilli are particularly important pathogens in older adults,

especially those with chronic underlying disease and those who are bedridden and recently hospitalized. *Pseudomonas* infection should be suspected in patients with pulmonary comorbidities and recent hospital stays.

Legionella spp. are the most important water-related pulmonary pathogens in the United States with regard to mortality and morbidity. The importance of *Legionella* spp. in causing pneumonia has varied greatly in different geographic areas, with incidences ranging from 0.6% to 23%.[193,194,197,203,213] Since 2003, an increased incidence of legionellosis has been observed in the United States, especially on the East Coast.[214] Although infection may occur at any age, those aged 45 to 64 now appear to be at greatest risk. The presence of a high fever (>40° C [104° F]), male sex, previous β-lactam therapy, multilobar involvement, rapid progression of radiographic abnormalities, a need for intensive care, gastrointestinal and neurologic abnormalities, elevated liver enzyme levels, and increased creatinine levels have all been associated with *Legionella* pneumonia.[194,213] However, no clinical features reliably distinguish *Legionella* pneumonia from that caused by other bacteria.

Moraxella catarrhalis has also been identified as a cause of pneumonia.[201-203,215] The overall incidence of disease caused by this bacterium is low, but it is an important pathogen in older adults with COPD and various forms of immunosuppression.

As discussed later, a number of additional pathogens, including *M. pneumoniae, Chlamydia* spp., *C. burnetii,* and community respiratory viruses can cause an atypical pneumonia syndrome. In addition, it is not infrequent for a patient to have pneumonia either sequentially or concurrently due to several pathogens, such as influenza virus or *C. pneumoniae* infection being followed by infection with *S. pneumoniae.*[203]

Community-Acquired Pneumonia in the Older Adult

Pneumonia in the elderly has become an increasingly important clinical entity as the world's population has aged.[216] Pneumonia is one of the leading reasons for hospitalization in those 65 and older and represents a major cause of morbidity and mortality. In some series, pneumonia represents the leading cause of death in this population (see Chapter 315). For those older than the age of 60, pneumonia is a predictor of increased mortality after the specific episode has resolved and for several years thereafter.[217]

The clinical presentation of pneumonia in older adults (especially those >80 years) may be subtler than in younger populations, with more gradual onset of symptoms and fever and the classic signs of pneumonia.[54,76,194] Fever occurs less commonly in older adults, and temperature elevation is muted. The classic findings of cough, fever, and dyspnea may be absent in over half of older adults.[75,218] Chills and rigors may be less frequently seen as well. Tachypnea (respiratory rate >24 to 30 breaths/min) and rales are more frequent findings in older adults and have been observed in up to 65% of patients.[54,76] Nonrespiratory symptoms may be the major presenting feature. The initial presentation of older adults with pneumonia may include decline in functional status, weakness, subtle changes in mental status, and anorexia or abdominal pain. It has been suggested that the nonspecific presentation of pneumonia in older adults may result in great part from the prevalence of dementia in this population.[218] Bacteremia, development of in-hospital complications, and death are more frequent in older populations.[76,219]

Specific etiologic diagnoses are made less frequently in older adults, with 20% to 50% of patients having an etiologic agent defined.[76] The absence of productive cough and common prior use of antibiotics may explain this observation. Causes have varied in different series depending on the means of diagnosis, the patient population studied (outpatient vs. institutionalized older adults), and the geographic location. In general, the cause of CAP in the older population follows the general trend of infection in younger populations. *S. pneumoniae* remains the predominant organism, accounting for 20% to 60% of cases, and there is an increased frequency of aspiration pneumonia.[76,216] *H. influenzae,* usually a nontypeable strain, is frequently the second most common agent, accounting for 5% to 10% of episodes.[76,220] The importance of other aerobic gram-negative bacilli in causing pneumonia in older adults remains a question, in part because the criteria for diagnosis of true pneumonia versus colonization vary. In most recent studies, 1% to 3% of cases of pneumonia have been attributed to non-*Haemophilus* gram-negative bacilli. Although increased oropharyngeal colonization with aerobic gram-negative bacilli has been documented in the older population and is believed to be a predisposition to development of pneumonia caused by these organisms, colonization appears to be related to debility of the patient rather than age.[221] Other factors reported to be associated with increasing colonization with gram-negative organisms include prior use of antibiotics, severe bronchopulmonary disease, decreased activity, alcoholism, and incontinence.[212] In this regard, one recent study of apparent aspiration pneumonia in a nursing home population older than 65 years of age that utilized protected bronchoalveolar lavage to define the microbiologic etiology identified gram-negative bacteria as the primary pathogen in 49%, followed by mixed anaerobes in 16%.[222] Older adults are at greater risk for infection with group B streptococci, *M. catarrhalis,* and *Legionella* species, although the overall incidence of these agents in the older population is relatively low. *Legionella* has been described as a cause of severe pneumonia in the elderly. Polymicrobial infections and pneumonia due to aspiration have both been noted to occur more frequently in older adults.[75,76]

It is unclear which agents cause atypical pneumonia in the older population. Most series suggest that *M. pneumoniae* pneumonia is unusual, although it has been documented by other investigators to be a significant cause of pneumonia leading to hospitalization in older adults.[55,75,76] It is not clear if this significant variation is related to differing epidemiologic characteristics of study populations or accuracy of diagnostic methods. *Chlamydia* infections appear commonly in the older population and may cause up to 32% of cases of pneumonia, although again there is a significant variation in incidence in differing studies.[55,76,223]

Viral agents play an important role as causes of pneumonia in the elderly, although historically their role has been underestimated, given the difficulty in culturing them and the relative insensitivity of serologic tests.[224] With the development of more sensitive nucleic acid amplification tests such as the reverse-transcriptase PCR assay, their role as causes of pneumonia has begun to be more clearly defined.[224,225] Recent studies have suggested a viral cause in up to one third of patients hospitalized with pneumonia, with significantly more viral infections noted in the older age groups (median age, 76 years).[225,226] Influenza A and B, RSV, human metapneumovirus, parainfluenza virus, and coronavirus are the most frequently identified viral pathogens. Recent studies indicate that up to half of the patients with a viral pathogen identified will have concurrent bacterial infection, and multiple concurrent viral pathogens also can be seen.[226] Rhinoviruses have not been defined as a direct cause of pneumonia but have been found in patients with severe pneumococcal disease and in vitro have shown increased adherence of *S. pneumoniae* to human tracheal epithelial cells.[226,227] These findings raise the question as to whether some viruses play a role as facilitators for bacterial infection rather than roles as true pulmonary pathogens.

Clinically, viral pneumonia in the elderly cannot be differentiated from bacterial pneumonia by clinical, routine laboratory, or radiologic parameters. As with bacterial disease, the signs of viral pneumonia may be subtle and may only involve fever and altered mental status.[224] Dyspnea, wheezing, and productive cough are commonly observed. Myalgia, while commonly found with most viral causes, is most often seen with influenza. Bronchospasm and wheezing may be more commonly seen with RSV.[224]

Nursing Home Pneumonia

Residents of skilled nursing facilities represent an important subpopulation of older adults at risk for pneumonia. Pneumonia has been reported to be the second most frequent infection in this setting, carries the highest mortality of any infection in this population, and is a common cause for hospitalization.[228,229] Silent aspiration is a major risk factor, as are poor functional status, nasogastric feeding, confusion, the presence of obstructive lung disease, the presence of a tracheostomy, and advancing age.[230] Key modifiable risk factors are inadequate oral care and swallowing difficulties.[231] The subtle presentation noted

in other older adult populations occurs in those in a nursing home setting. *S. pneumoniae* had been considered the predominant cause, but newer studies have identified respiratory viruses and *C. pneumoniae* as frequent pathogens, as well as *S. aureus* and gram-negative bacilli in those with severe pneumonia.[223,230] Outbreaks of pneumonia have occurred in nursing homes and have involved *Legionella, Chlamydia*, influenza, parainfluenza, RSV, and rhinovirus.[232,233]

Severe Community-Acquired Pneumonia

Approximately10% of patients with CAP will develop severe disease, as defined by admission to an ICU owing to the presence of shock requiring vasopressors or respiratory failure requiring mechanical ventilation.[234] Early identification of patients who are at higher risk for developing severe pneumonia is important because these patients have a higher mortality rate and require more supportive care. Furthermore, patients with severe pneumonia are infected with a different spectrum of etiologic agents and would therefore benefit from different empirical antibiotic strategies than patients with less severe disease. Advanced age, presence of significant comorbidities, nursing home residence, immunosuppression, and altered mental status have all been believed to be associated with the development of severe CAP.[234] Approximately one third of patients with severe pneumonia would have been previously healthy.

S. pneumoniae was the organism classically associated with severe pneumonia. However, in patients requiring ICU admission there is an increased incidence of *S. aureus, L. pneumophila,* gram-negative bacilli (especially *Klebsiella* spp.), and *H. influenzae*.[203,235,236] In addition, *Pneumocystis* is increasingly being recognized as a cause of severe pneumonia in non–HIV-infected patients who have impaired cell-mediated immunity due to organ transplantation, malignancy, severe malnutrition, or receipt of immunosuppressive therapies, including corticosteroids, antineoplastic chemotherapeutic agents, as well as newer agents including TNF-α inhibitors and rituximab.[237-239] As with CAP in general, there can be significant geographic differences in the relative incidence of differing pathogens.

A meta-analysis of 127 studies published through 1995 indicated an overall mortality rate for CAP of 13.7%, but it was 36.5% for patients with disease severe enough to require ICU care.[240] Prognostic risk factors for death included male sex, pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, diabetes mellitus, neoplastic disease, neurologic disease, bacteremia, leukopenia, and multilobar radiographic pulmonary infiltrates. Although shock or respiratory failure are usually evident and serve as major criteria for defining severe pneumonia, patients without these findings may also benefit from ICU care. During the past 2 decades a number of prediction rules have been developed to assess severity and prognosis of patients with pneumonia, including but not limited to the pneumonia severity index (PSI),[234] the confusion, urea, respiratory rate, low blood pressure (CURB) score,[241] the CURB plus age older than 65 (CURB-65),[242] the CURB-65 score without the urea level (CRB-65),[243] the severe community-acquired pneumonia (SCAP) score,[244] the SMART-COP score,[245] and the risk of early admission to the Intensive care unit (REA-ICU) index.[246] These rules vary in complexity as well as their sensitivity and specificity for defining the need for ICU care but use a combination of factors, including age, gender, comorbid conditions, vital sign parameters, and laboratory and radiographic findings, to predict either the need for ICU care or the patients' prognosis. Further use of these scoring systems is discussed under "Therapy."

Health Care–Associated Pneumonia

In the past, a basic distinction in the epidemiology of pneumonia has been whether the infection developed in the community or in the hospital. The distinction was clinically relevant because the importance of various etiologic agents differed, as did antibiotic susceptibilities. Consequently, the guidelines for empirical antibiotic therapy differed depending on where the infection developed. Because an increased amount of health care delivery has been shifted to the outpatient setting, even complex medical conditions may be handled without hospitalization. Subsequently, a growing number of patients develop pneumonia after extensive outpatient contact with various aspects of the health care system. This has led to a blurring of the distinction between CAP and nosocomial pneumonia. Recently, it has been recognized that HCAP represents a distinct syndrome that is a hybrid of CAP and hospital-acquired pneumonia (HAP).[77,78,247] The exact definition used in studies has varied, but in general it has been defined as pneumonia developing in patients who have been hospitalized for 2 or more days within 90 days of developing infection; patients attending hospital or hemodialysis clinics; patients receiving intravenous antibiotic therapy, wound care, or chemotherapy at home within 30 days of developing infection; and residents of long-term care facilities or nursing homes.[77] Aerobic gram-negative bacilli including *P. aeruginosa, S. pneumoniae, S. aureus* including MRSA, and mixed aerobic-anaerobic pathogens associated with aspiration have been most commonly reported.[78,248] The role of *S. pneumoniae* has been variable, but in general it appears to play a lesser role than in patients with classic CAP. Overall mortality appears to be higher in patients with HCAP (10.3% to 19.8%) than in CAP (4.3% to 10%) and generally comparable to that of HAP.[78,247,248] It is not clear whether this is due to increased comorbidities in patients, more virulent organisms causing infection, an increased incidence of inappropriate antibiotic usage in the first 48 hours of care, or some combination of these factors.

Atypical Pneumonia Syndrome

By the late 1930s, most of the main bacterial causes of pneumonia had been defined. In 1938, Hobart Reimann described a small number of patients with a clinical picture that was atypical in that episodes began as a mild respiratory tract illness that was followed by pneumonia with dyspnea and cough without sputum.[249] Subsequent investigations have shown that this syndrome can be seen with a number of different pathogens, with *M. pneumoniae, C. pneumoniae, L. pneumophila,* and respiratory viruses being the most significant. Other agents such as *Chlamydia psittaci, Francisella tularensis, M. tuberculosis,* and *C. burnetii* may also cause atypical pneumonia. In patients with AIDS, *Pneumocystis* and nontuberculous mycobacteria should also be included. Although some series report that almost 50% of patients with CAP demonstrate serologic evidence of mycoplasmal or chlamydial pneumonia, or both, other series suggest an incidence of 7% to 28%.[55,83,193,197,250-252] The differing incidence of mycoplasmal and chlamydial disease in differing studies may be related to the presence of epidemics by these pathogens during study periods, as well as the diagnostic methodologies utilized. As noted earlier, the relative frequency of these pathogens also varies with disease severity.

Historically, the epidemiology and clinical features of the atypical pneumonias were believed to be sufficiently distinct to differentiate them clearly from other causes of CAP. It is now clear that differentiation between atypical agents and typical bacterial causes of CAP is imprecise.[193]

M. pneumoniae may account for 10% to 30% of cases of CAP, with the highest percentage noted in patients well enough to be treated as outpatients, and several studies performed in North America and Europe suggest cyclic epidemics every 3 to 5 years.[147] It is most likely to occur in children older than 5 years, adolescents, and young adults. The majority of cases occur in those younger than 40 years of age, although it can cause pneumonia requiring hospitalization in those older than 60.[55,147,253] An increased incidence of disease and true epidemics has been documented in relatively enclosed populations of young adults at military bases, colleges, and boarding schools. Although the disease severity may be mild, owing to the long incubation of approximately 3 weeks, these outbreaks can be quite prolonged. Mycoplasmal infection occurs throughout the year, although a relative increase in incidence is noted in the late summer and fall.

The course of infection with *M. pneumoniae* is characterized by up to 10 days of symptoms before presentation, as is true with many of the other agents involved in atypical pneumonia. In its classic form, mycoplasmal infection presents as constitutional symptoms and a progression from the upper to the lower respiratory tract. Sore throat is often the initial finding. Up to one third of patients may have ear symptoms. Although bullous myringitis has been historically linked to mycoplasmal infection, this appears to be a rare finding. Fever, malaise, coryza, headache, and protracted nonproductive cough represent the major clinical findings. Pleuritic chest pain, splinting, and

respiratory distress are not usually seen. Moist or crepitant rales may be heard. Sputum production is variable, and the sputum is purulent in one third to one half of the cases. Gram stain and culture of sputum usually reveal mouth microbiota. White blood cell counts greater than 10,000/mm^3 are uncommon, occurring in approximately 20% of the patients.[90] An elevated sedimentation rate is noted in about 25% of the cases. Pulmonary involvement seen on radiographs is commonly more extensive than the physical examination would indicate. Unilateral or bilateral patchy infiltrates in one or more segments, usually in the lower lobes, are noted in a bronchial or peribronchial distribution. Upper lobe involvement and pleural effusions are less common but may be seen in up to 20% to 30% of cases.[185,186] Progression of the radiographic picture, despite a stable clinical picture, may be seen. The overall clinical course in most cases is benign. Disappearance of constitutional symptoms is usually noted in the first and second weeks, although cough and radiographic changes may persist for several weeks. Occasionally, *M. pneumoniae* infection presents as severe CAP that requires intensive care.[254] A large number of extrapulmonary manifestations may occur with *M. pneumoniae* infection, including involvement of skin, central nervous system, blood, and kidneys (see Chapter 185).

C. pneumoniae has emerged as an important cause of atypical pneumonia and may account for 6% to 20% of all CAP cases.[55,83,193,197,250-252] It is often seen in conjunction with other pathogens.[255] Although disease is uncommon in those younger than 5 years, serologic evidence of infection has been noted in more than 50% of adults, and more recent studies suggest an important role for *Chlamydia* in CAP in those older than 65 years of age.[55,76,223,256] Disease usually occurs sporadically, although epidemics have been well documented. The majority of infections are either asymptomatic or produce mild symptoms. As with mycoplasmal infection, sore throat and hoarseness herald the onset of pneumonia, although the progression of symptoms appears slower than that noted with mycoplasmal or viral pneumonia. Cough may begin after several days to weeks, suggesting a biphasic illness. Hoarseness and sinus tenderness appear more commonly than in patients infected with *Mycoplasma* or viruses. The white blood cell count is rarely elevated. Pneumonia with *C. pneumoniae* is usually mild, although complete recovery may be slow. Cough and malaise may persist for weeks to months. Reinfection occurs and appears to be milder than primary infection and is usually not associated with pneumonia. Chronic and latent infections have also been described. Infection with *C. pneumoniae* has been associated with exacerbations of COPD and asthma. In general, few features distinguish chlamydial pneumonia from infection caused by other atypical agents or other bacteria. *C. pneumoniae* infections have been associated with extrapulmonary manifestations, including otitis, sinusitis, pericarditis, myocarditis, and endocarditis. It has also been associated with coronary artery disease, although the definite relationship remains unclear (see Chapter 184).

Of the viral agents associated with atypical pneumonia in adults, influenza A and B, adenovirus types 3, 4, and 7 (especially in military recruits), human metapneumovirus, RSV (especially in older adult and immunosuppressed patients), and parainfluenza virus have been considered to be the most common.[182,183,224,225,257] The advent of multiplex real-time PCR assays is now rapidly expanding our understanding of the role of viral pathogens in acute pneumonia and has shown that rhinoviruses and coronaviruses can be significant pathogens in adults and that human bocavirus and human metapneumovirus are causative in children younger than 5 years of age.[258-261] Moreover, the presence of two or more viral pathogens is not uncommon. Other viral agents that are less common causes of pneumonia include enteroviruses, parechoviruses, all the herpesviruses, hantaviruses, mimiviruses, and measles.[262] Epidemic disease is predominantly linked to influenza, but the SARS coronavirus caused worldwide disease in 2002 and 2003, and a second similar coronavirus, the Middle East respiratory syndrome coronavirus (MERS-CoV), which can cause severe pneumonia, was identified in 2012 (see Chapter 157).[181] Elderly patients, especially those with comorbidities, are frequently the population at greatest risk for viral pneumonias.

Legionella is now recognized as an important cause of the atypical pneumonia syndrome, although patients infected with *Legionella* may also present with the syndrome of acute bacterial CAP. The incidence of pneumonia varies regionally, but it can account for up to 8% of cases involving hospitalization.[203] *Legionella* spp. are among the top three to four organisms causing pneumonia that require care in an ICU.[203,235,236] An international study found that *L. pneumophila* causes more than 90% of cases of *Legionella* pneumonia, with approximately 84% of all cases caused by *L. pneumophila* serogroup 1.[263] Inhalation of aerosolized organisms after exposure to environmental reservoirs, such as fresh water and moist soil, has been the usual means of acquiring the organism, although aspiration is now thought to be an alternate route of infection.[264]

Cigarette smoking, chronic lung disease, and immunosuppression are consistently noted risk factors for the development of disease. Although early symptoms of malaise, muscle aches, headaches, and nonproductive cough resemble the onset of a viral syndrome, the rapid progression of pulmonary symptoms and relatively high fever, often exceeding 40° C (104° F), is noteworthy.[264]

L. pneumophila pneumonia is associated with a variety of extrapulmonary findings and laboratory abnormalities, including mental status changes, abdominal complaints (loose stools or diarrhea), headache, bradycardia, elevation of hepatic enzyme levels, hypophosphatemia, hyponatremia, elevated serum lactate dehydrogenase levels, and elevated serum creatinine levels. These findings mostly reflect the severity of the pneumonia rather than specificity to *Legionella* infections. Extrapulmonary infection is unusual, but when it does occur it usually involves the heart, with myocarditis, pericarditis, and a postcardiotomy-like syndrome.[264] Unfortunately, none of these findings distinguishes between pneumonia due to *L. pneumophila,* other atypical agents, or more typical bacterial pathogens. Similarly, radiographic manifestations do not distinguish *Legionella* infections from those of other causes. Patchy interstitial infiltrates, or nodular infiltrates that may progress rapidly even with adequate therapy, are characteristic. Pleural effusions may be noted in up to one third of patients.

Pneumonia in the Setting of Aspiration

The clinical setting in which aspiration occurs includes any disease state in which consciousness is altered and the normal gag and swallowing reflexes are abnormal; illnesses predisposing to dysphagia either from neurologic disease or upper gastrointestinal tract disease or surgery; or conditions leading to mechanical disruption of glottic closure such as tracheostomy or nasogastric tubes. A recent prospective population-based study in a Canadian province analyzed 1946 patients hospitalized for pneumonia and identified aspiration as the cause in 10% of cases from the community and in 30% of cases from continuing care facilities.[265] In the community setting, 43% of the cases were related to an impaired level of consciousness due to alcohol, drugs, or hepatic failure and 35% of cases were due to dysphagia. In continuing care facilities, the predominant risk factor was dysphagia from neurologic disease in 72% of cases, with impaired level of consciousness the major risk factor for an additional 22% of patients.

The pathogenesis of lung injury due to acid aspiration has been delineated.[266,267] The presence of acidic contents in the lung induces the release of proinflammatory cytokines, including TNF-α and IL-8. These and other cytokines recruit neutrophils into the lung. Activated neutrophils appear to be the key mediators of acute lung injury after acid aspiration, although a role for complement has also been demonstrated.[268]

Although aspiration may be a witnessed event, the majority of episodes are silent and are brought to medical attention by their sequelae.[267] Three major syndromes are recognized as a consequence of aspiration: chemical pneumonitis, bronchial obstruction secondary to aspiration of particulate matter, and bacterial aspiration pneumonia. Aspiration may be associated with the acute respiratory distress syndrome, atelectasis, bronchial hyperreactivity, and fibrosis. Although chemical pneumonitis and mechanical obstruction usually cause acute symptoms, aspiration pneumonia is more insidious, with symptoms usually occurring gradually several days after the initial episode of aspiration. Pneumonitis, necrotizing pneumonia, abscess, and empyema are common. Symptoms often include fever, weight loss, and productive cough. Foul-smelling or putrid sputum occurs commonly.[269] Anemia and an elevated white blood cell count are frequent

associated findings. The bacteriologic findings in aspiration pneumonia reflect the microbiota of the oropharynx, and the importance of periodontal disease in this regard has been noted. Studies performed in the 1970s on patients with indolent disease using the technique of transtracheal aspiration and analysis in anaerobic research laboratories documented anaerobic involvement in the majority of cases either alone or in combination with oral aerobic or facultative anaerobes.[270] *Bacteroides* spp., *Porphyromonas* spp., *Prevotella melaninogenica, Fusobacterium* spp., and anaerobic gram-positive cocci are the predominant anaerobes isolated. In community-acquired aspiration pneumonia, *Streptococcus* spp. and *H. influenzae* are the most common aerobic isolates. In contrast, gram-negative bacilli (including *P. aeruginosa*) and *S. aureus* are the most commonly isolated aerobes from nosocomial aspiration pneumonia including VAP, as well as pneumonia occurring in nursing home patients.[77,222]

Eosinophilic Pneumonias

Pulmonary infiltrates with eosinophilia (PIE), also called eosinophilic pneumonia, is a syndrome associated with a variety of clinical entities, only some of which have an infectious cause.[271] Pulmonary eosinophilia with transient, peripheral pulmonary infiltrates and minimal symptoms (Löffler's syndrome) has been associated with *Ascaris, Strongyloides,* and hookworm infections. *Ascaris* is probably the leading parasitic cause of the syndrome worldwide. Prolonged pulmonary eosinophilia associated with weight loss, fever, cough, and dyspnea may be due to tuberculosis, brucellosis, psittacosis, coccidioidomycosis, histoplasmosis, and parasitic infections including ascariasis, strongyloidiasis, paragonimiasis, echinococcosis, visceral larval migrans, cutaneous larva migrans, and infections with *Schistosoma, Dirofilaria immitis,* and *Ancylostoma* species. Noninfectious causes include drug allergy, sarcoidosis, eosinophilic leukemia, Hodgkin's disease, paraneoplastic syndromes, and hypersensitivity pneumonitis (e.g., pigeon breeders' disease). A PIE syndrome has been associated with *Pneumocystis* pneumonia.[272]

Acute eosinophilic pneumonia is a distinct clinical entity occurring in younger (20- to 45-year-old), otherwise healthy individuals.[273] It is marked by the acute onset of dyspnea, nonproductive cough, fever, severe hypoxia, and chest pain and can require ICU care and mechanical ventilation. Although leukocytosis is common, peripheral eosinophilia is typically minimal. Bilateral, diffuse pulmonary infiltrates are common. Radiographic abnormalities usually begin as interstitial infiltrates that progress to alveolar infiltrates. Chest CT reveals bilateral opacities. BAL yields marked (27% to 81%) eosinophilia, which is the diagnostic feature of the disease. Although most patients have received antibiotics, rapid stabilization occurs with corticosteroid use.

It has been suggested that chronic eosinophilic pneumonia may represent a unique clinical entity that may be on a continuum between asthma and Churg-Strauss syndrome.[274] A subacute onset of cough, dyspnea, fever, and weight loss associated with peripheral eosinophilia are the common features. Unlike the situation in acute eosinophilic pneumonia, respiratory failure is rare. Peripheral as well as migratory infiltrates are commonly seen on radiographs. Interstitial infiltrate and alveolar exudates with a predominance of eosinophils are characteristic pathologic features. A rapid response to corticosteroids has been reported.

Tropical pulmonary eosinophilia consists of myalgia, fatigue, weight loss, and anorexia associated with cough, frequently with nocturnal exacerbations, wheezing, dyspnea, and marked peripheral eosinophilia in patients who have lived in or visited the tropics. Most cases are believed to represent immunologic hyperresponsiveness to microfilarial infection with *Wuchereria bancrofti* or *Brugia malayi.* Radiographic changes are distinctive and include increased interstitial markings with 2- to 4-mm nodules throughout the lungs with preferential involvement of the bases. Therapy is with diethylcarbamazine (see Chapter 289).

Other causes of PIE syndrome include bronchopulmonary mycosis, which should be suspected when a patient with PIE presents with asthma in conjunction with bronchiectasis, recurrent expectoration of brown mucus plugs, and peripheral eosinophilia.[271,275] Although predominantly associated with chronic bronchial colonization with *Aspergillus* species, it can be seen in conjunction with other fungi such as *Scedosporium apiospermum* and *Cladosporium herbarum.* Patients with the Churg-Strauss syndrome frequently have eosinophilia along with allergic angiitis and granulomatosis and present with asthma, diffuse pulmonary infiltrates, and multiorgan involvement. Hypereosinophilic syndrome, eosinophilic granuloma (also known as primary pulmonary Langerhans cell histiocytosis granulomatosis), bronchiolitis obliterans organizing pneumonia, Sjögren's syndrome, and postirradiation pneumonitis are unusual cases of pulmonary infiltrates with eosinophilia.

Hospital-Acquired Pneumonia

HAP has been the second most common cause of nosocomial infection and is associated with significant morbidity and mortality.[276,277] It is a leading cause of infection-related deaths in hospitalized patients, with attributable mortality rates of 20% to 33% reported. Higher mortality rates have been observed when patients are bacteremic or have pneumonia caused by *P. aeruginosa* or *Acinetobacter* spp. The morbidity associated with nosocomial pneumonia includes longer hospital stays (average, 7 to 9 days) and an estimated attributable cost of approximately $24,000.[77,278]

Risk factors for the development of nosocomial pneumonia have been categorized as patient related, infection control related, or intervention related. Patient-related risk factors include age older than 70 years, severe underlying disease, malnutrition, coma, metabolic acidosis, and the presence of any of a number of comorbid illnesses (e.g., COPD, alcoholism, azotemia, central nervous system dysfunction). Infection control–related risk factors include a lack of hand hygiene and glove-use practices and the use of contaminated respiratory equipment. Intervention-related risk factors involve those procedures and therapies that undermine normal host defenses or allow the host to be exposed to large inocula of bacteria. Sedatives and narcotics may lead to aspiration; corticosteroids and cytotoxic agents blunt the normal host response to infection; and the prolonged use of antibiotics engenders resistance. Surgical procedures, especially involving the chest and abdomen, are associated with changes in host defenses that predispose to pneumonia. The use of ventilator support is perhaps the greatest risk factor for the development of nosocomial pneumonia, with VAP occurring in 9% to 40% of intubated patients.[276] Data suggest that there is a 1% to 3% per day risk for developing pneumonia while on a ventilator, with a higher risk during the first 5 days of intubation.[279]

The use of antacids and H2 blockers that raise the gastric pH has been shown to increase stomach colonization with aerobic gram-negative rods.[280] Whether this leads to an increase in nosocomial pneumonia remains controversial.[36,37] The percentage of patients with VAP caused by organisms initially found in the stomach ranges from 0% to 55%.[280]

Aerobic gram-negative bacilli cause 50% to 60% of cases of nosocomial pneumonia, with members of the Enterobacteriaceae (*K. pneumoniae, Escherichia coli, Serratia marcescens, Acinetobacter* spp., *Enterobacter* spp.) and *Pseudomonas* species accounting for the majority of these.[74] There is an increasing prevalence of high-level antibiotic resistance among these gram-negative bacilli, and the relative incidence of pneumonia due to multidrug-resistant bacteria varies between institutions and occasionally between units within an institution.[276] Risk factors for such pathogens include the length of hospitalization, prior antibiotic exposure, and local epidemiologic factors. *S. aureus* causes 13% to 40% of nosocomial pneumonia, and MRSA is now a major pathogen in this setting.[74,77] In contrast to their prominent role in CAP, *S. pneumoniae* and *H. influenzae* together cause only 5% to 15% of nosocomial pneumonias in most studies and are predominantly seen in infections developing early in the hospital course. There is only limited information comparing the bacteriology of VAP and non–ventilator-associated HAP, but the available data indicate that the general distribution of aerobic pathogens is relatively comparable, although there is an increase in the relative prevalence of gram-negative pathogens in patients with VAP, particularly nonenteric gram-negative bacilli.[74,281] Although the use of sedatives, feeding tubes, and endotracheal tubes are all risk factors for the development of aspiration pneumonia, the lack of support for anaerobic microbiologic testing has led to a paucity of data on the roles of anaerobic bacteria in HAP.[267] One study performed in the early 1970s at a veterans hospital with bacteriologic analysis in a research laboratory documented anaerobes in up to

35% of cases of nosocomial pneumonia, and a second, more recent study identified anaerobes in conjunctions with aerobic microbiota in 23% of patients with VAP.[282,283] These organisms should be considered when aspiration is likely to have occurred. Pneumonia caused by *Legionella* species may occur sporadically or as part of outbreaks. The respiratory viruses influenza, parainfluenza, adenovirus, and RSV can cause sporadic nosocomial pneumonia as well as occasional institutional outbreaks. There has been the recognition that herpes simplex virus and cytomegalovirus can reactivate and be identified in patients with severe VAP or the adult respiratory distress syndrome. The significance of this reactivation remains uncertain at this time.[276]

Recent consensus guidelines have been established concerning the risks, etiology, diagnostic workup, and therapies for nosocomial pneumonia and VAP.[77] A more in-depth review is presented in Chapter 303.

Pneumonia in the Immunosuppressed Host

Pneumonia in the immunocompromised host is perhaps the most complex of all the pneumonia syndromes, because it represents the interaction of host defense defects engendered by the underlying disease as well as the chemotherapy of that disease, exposure to potential pathogens in the community and within the hospital setting, and reactivation of infectious processes that had previously been dormant. CAP, atypical pneumonia, aspiration pneumonia, and nosocomial pneumonia all take place in the compromised host. A large number of bacterial, fungal, viral, and noninfectious causes must be considered (see further discussion in Chapters 309 to 313).

THERAPY

The first decision confronting the clinician is whether the patient presenting with respiratory symptoms in fact has pneumonia. The difficulties in establishing a diagnosis on clinical grounds and the potential problem of overprescribing empirical antibiotics for all patients with respiratory findings have been reviewed. A chest radiograph is usually necessary to establish a definitive diagnosis of pneumonia and should be performed in patients considered ill enough to be considered for hospitalization.[284]

The next decisions are whether the patient is to be hospitalized and if so whether the patient needs admission to an ICU, both of which have consequences as to the level of treatment, the cost of care, and associated iatrogenesis. Inpatient management can increase the cost of care for CAP up to 25-fold, is less desirable to patients, and for low-risk patients is associated with comparable clinical outcomes.[285-287] Numerous severity assessment tools have now been developed to identify patients with more severe disease requiring hospitalization or ICU admission.[234,241-243,244-246] The earlier assessment tools incorporated a combination of clinical, epidemiologic, laboratory, and radiographic parameters to assess; and the more recently developed tools have focused on clinical parameters alone that can be evaluated at the bedside.

One of the earliest developed and most widely used assessment tool is the PORT score, also known as the pneumonia severity index (PSI).[234] This system uses 20 clinical parameters in categories of age, presence of comorbidities, vital sign abnormalities, and laboratory and radiologic findings. Based on a point system, five prognostic groups (I to V) were defined. The lowest scores (group I) are associated with low mortality (0.1%) and the highest scores (group V) are associated with the highest mortality (27%). As a guideline for hospitalization, patients in groups I and II are usually treated as outpatients, patients in group III are in a "borderline" group, and patients in groups IV and V are admitted to either a routine ward or ICU. The PORT score or PSI has been validated and widely endorsed.[84,288,289] A randomized controlled trial has confirmed that patients in PSI groups II or III who do not have respiratory failure, complicated pleural effusions, or unstable comorbid conditions have comparable clinical outcomes whether managed as inpatients or outpatients.[286] A limitation of the PSI system is its relative complexity, and several alternative scoring systems have now been developed that utilize more readily obtainable parameters. These include the CURB score, the CURB plus age greater than 65 score (CURB-65), and the CURB-65 score without the urea level (CRB-65).[241-243] The CURB score was formulated from the British Thoracic Society (BTS) study and uses four clinical parameters, which include new onset of confusion, urea level greater than 7 mmol/L, respiratory rate greater than 30 breaths/min, and systolic blood pressure less than 90 mm Hg or a diastolic blood pressure less than 60 mm Hg. The presence of two or more criteria suggested an increased mortality and defined severe pneumonia. The CURB-65 score, which was developed later, added age older than 65 years to the system with the presence of more than three parameters leading to prediction of increased mortality, and the CRB-65 modified this index to eliminate inclusion of blood urea determination, making the index free of laboratory testing and allowing for patient assessment completely at the bedside.

There have been several comparative trials of the various severity-assessment indices assessing their utility.[290] These indicate that the PSI, CURB-65, and CRB-65 tools appear relatively comparable in predicting high and low mortality groupings. Both the IDSA/ATS and BTS guidelines now support the use of these three severity illness scores for the assessment of patients with CAP.[84,284] The CRB-65 that does not require laboratory testing appears optimal for community or primary care settings.

There is evidence that the use of these severity assessment indices is increasing the percentage of patients with CAP who are receiving outpatient treatment.[291] However, it is critical to recognize that any severity assessment index serves only as a guideline, not as an absolute. Clinical judgment regarding presence of other comorbid conditions, hypoxia, stability of the home situation, ability to take oral medications, reliability in taking medication, likelihood of returning for follow-up, and likelihood of calling for help when needed all play a role in deciding whether a patient can be treated at home or in a hospital. In addition, the initial validation studies for the PSI, CURB-65, and CRB-65 indexes excluded patients who were HIV infected or otherwise immunocompromised or who had recently been hospitalized. There have recently been several studies on the utility of these indices for patients with HCAP that indicate that they can be used for such patients who are not immunocompromised,[292,293] but the data are still very limited for HCAP and these indices are not applicable for immunocompromised patients.

The PSI, CURB-65, and CRB-65 indices all predict the risk for mortality due to CAP and not the appropriate level of inpatient care required for a patient. As noted previously, approximately 10% of patients with CAP are admitted to ICUs. Several additional indices have more recently been devised to define those patients who could benefit from this level of care. These include the severe community-acquired pneumonia (SCAP) score, the SMART-COP score, and the risk of early admission to the intensive care unit (REA-ICU) index.[244-246] In addition, the IDSA/ATS guideline has recommended major and minor criteria to define patients who should be directly admitted to an ICU that have now been independently validated.[84,294] The major criteria are either septic shock requiring vasopressor support or acute respiratory failure requiring invasive mechanical ventilation. The presence of three of the following minor criteria also were indicative of the need for ICU care: increased respiratory rate greater than or equal to 30 breaths/min, low Pao_2/fraction of inspired oxygen ratio (≤250), multilobar infiltrates, confusion/disorientation, uremia (blood urea nitrogen level ≥20 mg/dL), leukopenia (white blood cell count <4000 cells/mm^3), thrombocytopenia (platelet count <100,000 cells/mm^3), hypothermia (core temperature <36°C [96.8°F]), and hypotension requiring aggressive fluid resuscitation. The complexity of these additional scoring systems limits their present utility, but the advent of more sophisticated electronic medical record systems that can incorporate diagnostic/therapeutic algorithms will assist in their use. Again, they remain guidelines and their application must be supplemented with clinical judgment.

Antimicrobial Therapy

Although mild cases can be self-limited, the use of antimicrobial agents is the mainstay of treatment of pneumonia. In reducing the microbial burden, antimicrobial therapy can reduce the duration of illness, risk for complications, and the mortality rate. If diagnostic studies, as described previously, yield a likely cause, specific narrow-spectrum therapy can be initiated. However, for most patients, a specific

diagnosis cannot be established with certainty prior to the onset of therapy and an antibiotic regimen must be selected empirically.

In addition to targeting the likely expected pathogens, primary considerations in selecting specific agents for treating pneumonia are the intrapulmonary penetration of differing agents and the pharmacokinetic and pharmacodynamic characteristics. With a few exceptions, most commercially available antimicrobial agents achieve adequate intrapulmonary concentrations to be used for treatment of pneumonia, although there can be significant differences in tissue penetration.[295] One agent, daptomycin, has been shown to bind to pulmonary surfactant, thereby decreasing its efficacy in treating pneumonia.[296]

Pharmacokinetics and pharmacodynamics are important in defining appropriate antibiotic dosing. β-Lactam compounds are time-dependent killers; when a penicillin, cephalosporin, or carbapenem is being used, the active drug levels need to be above the minimal inhibitory concentration (MIC) of the organism being treated for 40% to 50% of the dosing interval for an optimal outcome.[297,298] Parenteral administration of aminoglycosides leads to low concentration in bronchial fluids, and when given using traditional dosing serum peak levels of at least 6 μg/mL for gentamicin or tobramycin and 24 μg/mL for amikacin are needed for successful outcomes in treating gram-negative pneumonia.[299] However, as aminoglycosides show concentration-dependent killing with a significant postantibiotic effect, improved clinical outcomes can be achieved by using pharmacodynamic modeling to optimize dosing.[297,300] A retrospective pharmacodynamic/pharmacokinetic analysis of the efficacy of vancomycin for treatment of *S. aureus* pneumonia indicated that clinical cure correlates with a 24-hour area under the curve (AUC)/MIC ratio of greater than or equal to 400 and indicates that optimal dosing should target a vancomycin trough level of 15 to 20 μg/mL.[301,302] Unfortunately, even this high-level vancomycin therapy may not be effective in treating strains of *S. aureus* that have MICs greater than or equal to 2 μg/mL.[303]

The empirical antimicrobial regimen selected to treat acute pneumonia is dependent on the clinical situation. Several professional societies including the IDSA, the ATS, the BTS, and the Pediatric Infectious Disease Society have now developed guidelines for management of CAP, and the IDSA and ATS have published joint guidelines on managing HAP, VAP, and HCAP in adults.[77,84,284,304,305] For adults with CAP, the IDSA/ATS guidelines and BTS both recommend stratifying patients for outpatient versus inpatient treatment based on PSI or CURB-65 scoring systems, although the BTS recommends the use of the CRB-65 score for patients seen in the community or primary care setting. In all of the guidelines, recognition of the most likely etiologic agent in any given clinical situation and recognition of the organisms most likely to cause morbidity and mortality are emphasized. Finally, prevalence of common antibiotic resistance patterns and risks of acquisition are recognized. Empirical antibiotic therapy for CAP in children and adults, as well as for HCAP, is reviewed in Tables 69-4 and 69-5. The reader is referred to Chapter 303 for recommendations for empirical management of HAP.

For a patient who does not require hospitalization and for whom no clear distinction between typical (e.g., pneumococcal) and atypical (mycoplasmal, chlamydial) pneumonia can be made, both types of organisms should be covered. Risks for the presence of drug-resistant *S. pneumoniae* should be assessed. Use of previous antibiotics, especially a β-lactam, macrolide, or fluoroquinolone in the prior 3 to 6 months, as well as residence in a long-term care facility are predictive of the presence of resistance to β-lactams, macrolides, and fluoroquinolones.[306-308] Where risk for drug-resistant *S. pneumoniae* infection is low, oral β-lactam agents (high-dose amoxicillin, amoxicillin-clavulanate, cefuroxime axetil), azalides/macrolides (azithromycin, clarithromycin, or erythromycin), or respiratory tract quinolones (levofloxacin, gemifloxacin, moxifloxacin) are all adequate choices. Doxycycline and trimethoprim-sulfamethoxazole may be used, but there is concern for an increasing incidence of resistance to both of these agents in strains of pneumococci.[84,284] Increased resistance to the azalide/macrolide agents due to blockage of the ribosomal binding area encoded by the *ermB* gene is also becoming a problem in *S. pneumoniae,* and therapeutic failures have been noted.[309] Although it has been suggested that these agents may be used as long as the resistance rate is less than 25%, recent analysis suggests that that resistance level is too high and will be associated with increased morbidity and mortality.[310]

For patients with an increased risk for poor outcome because of age or underlying disease, or when the risk for infection with resistant pneumococci exists owing to prior antibiotic use, the respiratory tract quinolones are the agents most likely to be effective. They currently are active against more than 99% of strains of *S. pneumoniae,* including penicillin-resistant strains, and they have the added benefit of activity against atypical agents. Although increasing resistance is a potential problem with an increased use of quinolones, it has not yet emerged as a significant problem. A β-lactam plus a macrolide is a comparable regimen.

Regardless of the initial choice of antibiotic, once an organism is isolated, coverage should be narrowed down, if possible, on the basis of susceptibility test results.

Patients who are ill enough to require hospitalization should be treated with parenteral agents that cover the likely pathogens. Whether there is a benefit for antibiotic combinations in this setting remains an ongoing question. Combination therapy with β-lactam antibiotics and macrolides, especially azithromycin, had been associated in some studies with decreased mortality and decreased length of hospital stay. However, this benefit has been decreased or not apparent in randomized controlled trials or studies addressing guideline-concordant therapy.[311-313] In addition, the potential slight benefit of combination therapy with azithromycin is counterbalanced by a small increased risk for sudden death due to cardiovascular events in individuals with preexisting cardiovascular risk factors.[314-316] Our choice for most individuals would be a β-lactam (ceftriaxone or cefotaxime) plus azithromycin except in patients at high risk for cardiovascular disease when a respiratory fluoroquinolone seems preferable. If there are factors that suggest a specific etiology, or a Gram stain is revealing, specific antibiotic coverage should be used.

Although these regimens represent the basic course of therapy, specific clinical circumstances may warrant variation. For example, *S. aureus* pneumonia including community-associated MRSA should be considered during an influenza outbreak even though *S. pneumoniae* is still the major etiologic agent. Agents with activity against MRSA should be utilized if there is reason to suspect its presence as the cause of pneumonia. Linezolid and vancomycin are the best-studied agents for treatment of MRSA pneumonia, and clindamycin has also appeared effective in children.[305,317] A prospective controlled trial comparing linezolid and vancomycin with HAP or HCAP due to MRSA found a better initial clinical outcome for patients treated with linezolid but no difference in mortality at 60 days.[318] A new cephalosporin, ceftaroline, has good in vitro activity against MRSA isolates and may prove to be another alternative for treatment of MRSA pneumonia, although clinical trials of its use in this setting are not currently available.[319] Should the patient be found to have methicillin-susceptible *S. aureus* pneumonia, treatment with nafcillin or oxacillin is preferred. Current clinical efficacy data on the use of trimethoprim-sulfamethoxazole, fluoroquinolones, doxycycline, or tigecycline for treatment of staphylococcal pneumonia are not available.

Where anaerobic aspiration pneumonia is a possibility, such as in patients developing pneumonia after loss of consciousness due to drugs, alcohol, or neurologic disease, agents with activity against oral anaerobes are needed, including ampicillin-sulbactam or clindamycin. Otherwise, clinical trials suggest that targeted anaerobic coverage is not required for the majority of cases of CAP.[84]

Aerobic gram-negative bacilli including *P. aeruginosa* cause 7% to 18% of CAP cases. Risk factors previously noted for gram-negative pneumonia should therefore be sought. When gram-negative bacilli are suspected, infection with *P. aeruginosa* should be a concern and therapy with an antipseudomonal β-lactam compound (e.g., cefepime, ceftazidime, piperacillin-tazobactam, imipenem, or meropenem) is a reasonable choice. When *Pseudomonas* involvement can be excluded, agents such as cefotaxime, ceftriaxone, or ertapenem could be considered. Debate exists as to whether combination therapy with both a β-lactam agent and either an aminoglycoside or quinolone will improve the outcome of gram-negative pneumonia. Data exist to support both sides of the controversy, although there is increasing evidence that initial combination therapy decreases the risk for initially

TABLE 69-4 Guide to Empirical Choice of Antimicrobial Agent for Treating Adult Patients with Community-Acquired Pneumonia or Health Care–Acquired Pneumonia

PATIENT CHARACTERISTICS	PREFERRED TREATMENT OPTIONS
Outpatient	
Previously Healthy	
No recent antibiotic therapy	Macrolide[a] or doxycycline (100 mg 2 times/day)
Recent antibiotic therapy[b]	A respiratory fluoroquinolone[c] alone, an advanced macrolide[d] plus oral β-lactam[e]
Comorbidities (COPD, Diabetes, Renal Failure or Congestive Heart Failure, or Malignancy)	
No recent antibiotic therapy	An advanced macrolide plus oral β-lactam or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin (600 mg IV q8h or 300 mg PO q6h)
Influenza with bacterial superinfection	Vancomycin, linezolid, or other coverage for MRSA, including community-acquired MRSA[f]
Inpatient	
Medical Ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus an intravenous β-lactam[g]
Recent antibiotic therapy	An advanced macrolide plus an intravenous β-lactam, or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
Intensive Care Unit (ICU)	
Pseudomonas infection is not a concern	A β-lactam[g] plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not a concern but patient has a β-lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
Pseudomonas infection is a concern[h] (cystic fibrosis, impaired host defenses)	Either (1) an antipseudomonal β-lactam[i] plus ciprofloxacin (400 mg IV q8h or 750 mg PO q12h), or (2) an antipseudomonal agent plus an aminoglycoside[j] plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is a concern but the patient has a β-lactam allergy	Aztreonam (2 g IV q8h) plus aminoglycoside plus a respiratory fluoroquinolone
Health Care–Associated Pneumonia[k]	
—	Either (1) an antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or (2) an antipseudomonal agent plus an aminoglycoside plus a respiratory fluoroquinolone or a macrolide plus vancomycin or linezolid (for MRSA coverage)

[a]Azithromycin, clarithromycin, or erythromycin.

[b]That is, the patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection. Such treatment is a risk factor for drug-resistant *Streptococcus pneumoniae* and possibly for infection with gram-negative bacilli. Depending on the class of antibiotics recently given, one or another of the suggested options may be selected. Recent use of a fluoroquinolone should dictate selection of a nonfluoroquinolone regimen and vice versa.

[c]Moxifloxacin (400 mg once daily), gemifloxacin (320 mg once daily), or levofloxacin (750 mg once daily).

[d]Azithromycin (500 mg once daily), clarithromycin (250-500 mg twice daily), erythromycin (250-500 mg four times a day).

[e]High-dose amoxicillin (1 g three times a day), high-dose amoxicillin-clavulanate (2 g twice daily), cefpodoxime (200 mg twice daily), or cefuroxime (500 mg twice daily).

[f]Vancomycin dosing should target a vancomycin trough level of 15 to 20 μg/mL; linezolid (600 mg twice daily).

[g]Cefotaxime (1-2 g IV q4-8h), ceftriaxone (1 g IV daily), ampicillin (1-2 g IV q4-6h), ampicillin-sulbactam (1.5-3 g IV q6h), or ertapenem (1 g IV daily).

[h]Risk factors for *Pseudomonas* infection include severe structural lung disease (e.g., bronchiectasis) and recent antibiotic therapy, health care–associated exposures or stay in hospital (especially in the ICU). For patients with community-acquired pneumonia in the ICU, coverage for *S. pneumoniae* and *Legionella* species must always be considered.

[i]Piperacillin (3 g IV q4h), piperacillin-tazobactam (3.375 g IV q6h), imipenem (500-1000 mg IV q6h), meropenem (1-2 g IV q8h), ceftazidime (2 g IV q6-8h), or cefepime (1-2 g IV q8h) are excellent β-lactams and are adequate for most *S. pneumoniae* and *H. influenzae* infections. They may be preferred when there is concern for relatively unusual pathogens of community-acquired pneumonia, such as *P. aeruginosa, Klebsiella* species, and other gram-negative bacteria.

[j]Data suggest that older adults receiving aminoglycosides have worse outcomes. Traditionally dosed aminoglycosides should achieve peak levels of at least 8 μg/mL for gentamicin or tobramycin and 25-35 μg/mL for amikacin and troughs less than 2 μg/mL for gentamicin and tobramycin and less than 10 μg/mL for amikacin. Once-daily dosing for gentamicin or tobramycin is 7 mg/kg IV with trough target <1 μg/mL, and 20 mg/kg IV for amikacin with trough target <4 μg/mL.[77]

[k]Pneumonia developing in patients who have been hospitalized for 2 or more days within 90 days of developing infection; patients attending hospital or hemodialysis clinics; patients receiving intravenous antibiotic therapy, wound care, or chemotherapy at home within 30 days of developing infection; and residents of long-term care facilities or nursing homes.

COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *S. aureus*.

Note: All dosages are usual adult doses and may require adjustment in relation to renal or hepatic function, a patient's body mass index, or drug-drug interactions.

Modified from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. *2007;44(suppl 2):S27-S72; and American Thoracic Society, 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. *2005;171:388-416.*

TABLE 69-5 Guide to Empirical Choice of Antimicrobial Agent for Treating Children with Community-Acquired Pneumonia

PATIENT CHARACTERISTICS	PREFERRED TREATMENT OPTIONS
Outpatient	
<5 Years of Age	
Presumed bacterial	Oral amoxicillin (90 mg/kg/day) in 2 doses or oral amoxicillin-clavulanate (90 mg/kg/day amoxicillin component) in 2 doses
Presumed atypical	Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day on days 2-5) or oral clarithromycin (15 mg/kg/day in 2 doses or oral erythromycin (40 mg/kg/day in 4 doses
≥5 Years of Age	
Presumed bacterial	Oral amoxicillin (90 mg/kg/day in 2 doses to a maximum of 4 g/day) or oral amoxicillin-clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses to a maximum dose of 4000 mg/day); add macrolide if cannot distinguish bacterial or atypical
Presumed atypical	Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2-5 to a maximum of 500 mg on day 1, followed by 250 mg on days 2-5) or oral clarithromycin (15 mg/kg/day in 2 doses to a maximum of 1 g/day) or erythromycin or doxycycline for children >7 yr old

Continued

TABLE 69-5 Guide to Empirical Choice of Antimicrobial Agent for Treating Children with Community-Acquired Pneumonia—cont'd

PATIENT CHARACTERISTICS	PREFERRED TREATMENT OPTIONS
Inpatient (All Ages)	
***Fully Immunized against* S. pneumoniae *and* H. influenzae*, and Low Local Level of Antibiotic Resistance in* S. pneumoniae**	
Presumed bacterial	Ampicillin or penicillin G or ceftriaxone or cefotaxime; add vancomycin or clindamycin for suspected community-associated MRSA
Presumed atypical	Azithromycin (add β-lactam, if diagnosis of atypical pneumonia is in doubt); or clarithromycin or erythromycin; or doxycycline for children >7 yr old; or levofloxacin for children who have reached growth maturity or who cannot tolerate macrolides
***Not Fully Immunized against* S. pneumoniae *and* H. influenzae*, or High Local Level of Antibiotic Resistance in* S. pneumoniae**	
Presumed bacterial	Ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected community-associated MRSA; alternative: levofloxacin; addition of vancomycin or clindamycin for suspected community-associated MRSA
Presumed atypical	Azithromycin (add β-lactam if diagnosis in doubt); or clarithromycin or erythromycin; or doxycycline for children >7 yr old; or levofloxacin for children who have reached growth maturity or who cannot tolerate macrolides

MRSA, methicillin-resistant *S. aureus.*

Adapted from Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. *2011;53:e25-e76.*

inappropriate therapy.[320,321,322,323] We favor initial combination therapy for patients who are severely ill, at least until culture results from sputum and blood are available to confirm that an agent is being given with in vitro activity against the presumed organisms. In patients who are allergic to penicillin, aztreonam with a respiratory tract fluoroquinolone, with or without an aminoglycoside, could be used.

In the patient admitted to an ICU, therapy should be directed against *S. pneumoniae,* penicillin-resistant strains, *Legionella* spp., gram-negative rods, and *M. pneumoniae.* If infection with *P. aeruginosa* is unlikely (no recent hospitalization, no recent antibiotic use, no pulmonary comorbidities, no gram-negative rods on Gram stain), a β-lactam plus either an azalide/macrolide or a respiratory tract fluoroquinolone would be therapies of first choice. Ceftriaxone or cefotaxime would be reasonable choices for the β-lactam. When *Pseudomonas* infection cannot be excluded, an antipseudomonal β-lactam (cefepime, imipenem, meropenem, doripenem, or piperacillin-tazobactam) plus a respiratory tract fluoroquinolone or azalide/macrolide could be used. We favor cefepime or piperacillin-tazobactam plus a respiratory tract fluoroquinolone. An aminoglycoside could be added as a third agent for synergy against *Pseudomonas.* Evidence in the literature favoring one regimen over any other is lacking.

Timing of Antibiotics

In 1997, a retrospective review of more than 14,000 Medicare patient hospitalizations suggested that antibiotic therapy given within 8 hours of presentation was associated with a decreased mortality.[324] A second retrospective study of similar design in 2004 showed that antibiotics given within 4 hours of presentation would result in lower mortality.[325] Neither study corrected for the cause of the pneumonia nor the antibiotics used. Despite the lack of a prospective randomized study, advising and regulatory agencies, including the Joint Commission and the Centers for Medicare and Medicaid Services, began to use the 4-hour rule as a core quality measure. Subsequent studies found that attempting to meet this performance standard led to increased misdiagnoses and potentially inappropriate antibiotic prescribing in emergency department patients, and failure of hospitals to meet this standard was not associated with an increase in inpatient mortality in patients admitted with CAP.[326-328] This hospital performance standard has subsequently been eliminated. Still, there is strong evidence that delays in antibiotic therapy can impact the outcome of patients with sepsis.[329] The IDSA/ATS guidelines currently recommend that antibiotic therapy for pneumonia should be started as soon as the diagnosis is considered likely.[84]

Duration of Treatment and Use of Clinical Practice Guidelines

Until recently, the duration of antibiotic therapy for pneumonia has been based on anecdotal patterns of behavior. There have been few studies addressing the appropriate duration of treatment, but the classic 10- to 14-day duration of care is unsupported by evidence.[330] Recent data now indicate that clinical stability (defined as normalization of previously abnormal physiologic parameters, including heart rate, respiratory rate, oxygenation, blood pressure, mental state, and ability to care for oneself) occurs relatively quickly for patients hospitalized with CAP (see Table 69-6).[331] Most physiologic abnormalities will correct in 2 to 3 days, and normalization of all physiologic abnormalities generally occurs in 5 to 7 days. Patients with more severe illness generally take longer to stabilize. The addition of monitoring for an at least 50% reduction in C-reactive protein has been suggested as an additional measure to define clinical stability but appeared beneficial only for patients with severe disease, and the cost-effectiveness of this approach has not been assessed.[332] Overall, once stability is achieved, clinical relapses serious enough to require ICU care occur less than 1% of the time.

TABLE 69-6 Evidence of Clinical Stability

Temperature ≤37.8°C (100°F)
Pulse ≤100 beats/min
Respiratory rate ≤24 breaths/min
Systolic blood pressure ≥90 mm Hg
Arterial oxygen saturation ≥90% or Po_2 ≥60 mm Hg on room air
Ability to maintain oral intake
Normal mental status

Data from Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA. *1998;279:1452-1457; and Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults.* Clin Infect Dis. *2007;44(suppl 2):S27-S72.*

Oral antibiotic therapy is safe after clinical stability has been reached even in patients with severe CAP.[333-335] There is no clear usefulness of observing a patient within the hospital after a switch to oral therapy.[336] However, it is important to recognize that discharging patients before stability has been reached may lead to increased rehospitalization and death.[337,338] Using the same definitions of clinical stability, it has been shown that the greater the number of factors remaining abnormal at discharge, the greater is the chance of readmission or death.

There are few studies on the duration of therapy for pneumonia that are prospective, well-controlled, use the same antibiotic and dosing schedule, and only vary the duration of therapy. However, these few studies have found that a period of less than 7 days and as short as 3 days of azithromycin is just as effective as longer durations of therapy for mild to moderate CAP.[339,340] With age, presence of underlying comorbidities including immune compromise, and more virulent pathogens, clinical stability may be delayed; therefore, duration of antibiotic therapy may be lengthened. Currently, for adult patients with

CAP the IDSA/ATS guidelines recommend a minimum of at least 5 days of antibiotic therapy, with the patient being afebrile for between 48 and 72 hours and lacking no more than one sign of clinical stability.[84] Similarly, the BTS guidelines recommend 7 days of appropriate antibiotic therapy for patients with low- or moderate-severity CAP treated either as outpatients or inpatients.[284] Longer therapy should be considered for patients who have high-severity disease, bacteremic *S. aureus* pneumonia, or cavitary disease. The Pediatric Infectious Disease Society/IDSA guidelines for CAP in children note that 10 days of treatment is best studied in children, although shorter course treatment is likely effective.[305]

Although early studies found limited benefit to concordance of process of care measures and clinical outcomes in pneumonia, more recent evidence indicates that compliance with clinical practice guidelines for both CAP and HCAP is associated with decreased inpatient mortality and inpatient length of stay.[142,312,313,341-344] The use of inpatient critical pathways based on clinical practice guidelines can reduce inpatient length of stay without increasing adverse effects.[288,345,346]

Once discharged, outpatient follow-up should be coordinated, because most patients with CAP will have some related residual symptoms, including fever, cough, shortness of breath, chest pain, sputum production, fatigue, or gastrointestinal symptoms. Comorbidities, particularly cardiopulmonary or neurologic disease, are the most frequent reason for subsequent early readmission among patients who achieve clinical stability.[338,347]

Adjunctive Therapy

A robust inflammatory response to an invading pathogen can lead to a potentially worse outcome in pneumonia, and the use of anti-inflammatory agents could have potential benefits, as demonstrated with the improved outcome with the addition of corticosteroid therapy for *Pneumocystis* pneumonia. The macrolide family has been shown to have in vitro immunomodulatory activity, which may contribute to their efficacy in CAP.[348] A number of randomized controlled trials have now investigated the efficacy of corticosteroid therapy for CAP using differing dosages and agents. To date there is no evidence of an impact on overall mortality, although corticosteroids may shorten overall inpatient length of stay by 1 day.[349,350] Statins also possess anti-inflammatory properties, and their impact on CAP has been assessed in observational studies. Although there was initial suggestive evidence of benefit, those studies were not randomized and did not control for other potentially important variables, such as underlying health or socioeconomic status.[351] A more recent study that controlled for these factors found no impact of recent statin use on the incidence of severe sepsis or mortality from CAP.[352] Although other adjunctive therapies have been described, including the use of activated protein C, noninvasive mechanical ventilation, anticoagulants, immunoglobulin, granulocyte colony-stimulating factor, probiotics, chest physiotherapy, antiplatelet drugs, over-the-counter cough medications, β_2-agonists, inhaled nitric oxide, and angiotensin-converting enzyme inhibitors, in clinical trials none of these approaches has been shown to have a significant role in therapy.[353]

PREVENTION

Vaccination against influenza and *S. pneumoniae* are important interventions in preventing pneumonia. In older adults, influenza vaccine can decrease the incidence of hospitalization, pneumonia, and mortality; and efficacy has been demonstrated over 10 consecutive influenza seasons.[354,355] Influenza vaccine is suggested for any person 6 months of age or older who, because of age or underlying disease, is at risk for influenza-related complications. This includes persons older than 50 years; nursing home residents; people with chronic pulmonary or cardiac disease, or with chronic diseases such as diabetes, renal failure, or hematologic disorders; patients who are immunosuppressed; those taking chronic salicylate therapy; and women in their second or third trimester of pregnancy. Health care workers, workers in nursing homes, and those who provide care to older adults or debilitated persons should also be targeted for influenza vaccination.[356]

A 23-valent pneumococcal polysaccharide vaccine and both 7-valent and 13-valent pneumococcal conjugate vaccines are licensed in the United States. Although there are good clinical data showing that these vaccines provide protection against bacteremia and invasive pneumococcal disease, there are as yet no data showing the efficacy of these vaccines in preventing pneumonia.[357,358] Both the 23-valent pneumococcal polysaccharide and the 13-valent pneumococcal conjugate vaccines have now been approved for use in adults older than 50 years of age, and pneumococcal vaccine is recommended for patients older than 65 and those who have recovered from CAP. Further discussion of the efficacy of these vaccines is provided in Chapter 201.

Active smoking is a clear risk factor for bacterial pneumonia, and promoting smoking cessation should be a component of pneumonia prevention.[60,359,360]

Key References

The complete reference list is available online at Expert Consult.

20. Mizgerd JP. Acute lower respiratory tract infection. *N Engl J Med*. 2008;358:716-727.
53. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA*. 1997;278:1440-1445.
54. Metlay JP, Schulz R, Li YH, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med*. 1997;157:1453-1459.
55. Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med*. 1997;157:1709-1718.
56. Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. *JAMA*. 2013;309:275-282.
62. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. *Scand J Infect Dis*. 2011;43:609-615.
69. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medical Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed May 7, 2013.
76. Fernandez-Sabe N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine (Baltimore)*. 2003;82:159-169.
77. American Thoracic Society, 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*. 2005;171:388-416.
78. Carratala J, Mykietiuk A, Fernandez-Sabe N, et al. Health care–associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med*. 2007;167:1393-1399.
83. Johansson N, Kalin M, Tiveljung-Lindell A, et al. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis*. 2010;50:202-209.
84. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S72.
85. Roson B, Carratala J, Verdaguer R, et al. Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. *Clin Infect Dis*. 2000;31:869-874.
87. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis*. 2004;39:165-169.
99. Murdoch DR. Diagnosis of *Legionella* infection. *Clin Infect Dis*. 2003;36:64-69.
118. Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med*. 2006;355:2619-2630.
128. Light RW. Parapneumonic effusions and empyema. *Proc Am Thorac Soc*. 2006;3:75-80.
131. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. *Clin Infect Dis*. 2007;45:1480-1486.
139. Falguera M, Trujillano J, Caro S, et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. *Clin Infect Dis*. 2009;49:409-416.
147. Waites KB, Talkington DF. *Mycoplasma pneumoniae* and its role as a human pathogen. *Clin Microbiol Rev*. 2004;17:697-728.
152. Smith JA, Kauffman CA. Pulmonary fungal infections. *Respirology*. 2012;17:913-926.
154. Onishi A, Sugiyama D, Kogata Y, et al. Diagnostic accuracy of serum 1,3-beta-D-glucan for *Pneumocystis jiroveci* pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. *J Clin Microbiol*. 2012;50:7-15.
163. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2012;(9):CD007498.
174. Boersma WG, Daniels JM, Lowenberg A, et al. Reliability of radiographic findings and the relation to etiologic agents in community-acquired pneumonia. *Respir Med*. 2006;100:926-932.
193. Marrie TJ, Peeling RW, Fine MJ, et al. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. *Am J Med*. 1996;101:508-515.
194. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. *Medicine (Baltimore)*. 1990;69:307-316.
197. Bochud PY, Moser F, Erard P, et al. Community-acquired pneumonia: a prospective outpatient study. *Medicine (Baltimore)*. 2001;80:75-87.
199. Fine MJ, Stone RA, Singer DE, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med*. 1999;159:970-980.

222. El-Solh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med*. 2003;167:1650-1654.
225. Johnstone J, Majumdar SR, Fox JD, et al. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest*. 2008;134:1141-1148.
234. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243-250.
242. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377-382.
243. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J*. 2006;27:151-157.
255. File TM Jr, Plouffe JF Jr, Breiman RF, et al. Clinical characteristics of *Chlamydia pneumoniae* infection as the sole cause of community-acquired pneumonia. *Clin Infect Dis*. 1999;29:426-428.
258. Lieberman D, Shimoni A, Shemer-Avni Y, et al. Respiratory viruses in adults with community-acquired pneumonia. *Chest*. 2010;138:811-816.
262. Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. *Lancet*. 2011;377:1264-1275.
264. Stout JE, Yu VL. Legionellosis. *N Engl J Med*. 1997;337:682-687.
265. Reza Shariatzadeh M, Huang JQ, Marrie TJ. Differences in the features of aspiration pneumonia according to site of acquisition: community or continuing care facility. *J Am Geriatr Soc*. 2006;54:296-302.
276. Barbier F, Andremont A, Wolff M, et al. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. *Curr Opin Pulm Med*. 2013;19:216-228.
284. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009;64(suppl 3):iii1-iii55.
302. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82-98.
304. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;66(suppl 2):ii1-ii23.
305. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53:e25-e76.
321. Heyland DK, Dodek P, Muscedere J, et al; Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med*. 2008;36:737-744.
324. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278:2080-2084.
331. Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA*. 1998;279:1452-1457.
338. Capelastegui A, Espana Yandiola PP, Quintana JM, et al. Predictors of short-term rehospitalization following discharge of patients hospitalized with community-acquired pneumonia. *Chest*. 2009;136:1079-1085.
345. Fine MJ, Stone RA, Lave JR, et al. Implementation of an evidence-based guideline to reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized with community-acquired pneumonia: a randomized controlled trial. *Am J Med*. 2003;115:343-351.
355. Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007;357:1373-1381.

References

1. Osler W. *The Principles and Practice of Medicine*. 4th ed. New York: Appleton; 1901.
2. Minino AM, Murphy SL, Xu J, et al. Deaths: final data for 2008. *Natl Vital Stat Rep*. 2011;59:1-126.
3. Charlson ES, Bittinger K, Haas AR, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med*. 2011;184:957-963.
4. Erb-Downward JR, Thompson DL, Han MK, et al. Analysis of the lung microbiome in the "healthy" smoker and in COPD. *PLoS One*. 2011;6:e16384.
5. Sze MA, Dimitriu PA, Hayashi S, et al. The lung tissue microbiome in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;185:1073-1080.
6. Reynolds HY. Pulmonary host defenses: state of the art. *Chest*. 1989;95(3 suppl):223S-230S.
7. Sibille Y, Reynolds HY. Macrophages and polymorphonuclear neutrophils in lung defense and injury. *Am Rev Respir Dis*. 1990;141:471-501.
8. Ganz T. Antimicrobial polypeptides in host defense of the respiratory tract. *J Clin Invest*. 2002;109:693-697.
9. Wright JR. Immunomodulatory functions of surfactant. *Physiol Rev*. 1997;77:931-962.
10. Zhang P, Summer WR, Bagby GJ, et al. Innate immunity and pulmonary host defense. *Immunol Rev*. 2000;173:39-51.
11. Lohmann-Matthes ML, Steinmuller C, Franke-Ullmann G. Pulmonary macrophages. *Eur Respir J*. 1994;7:1678-1689.
12. Little FF, Wilson KC, Berman JS, et al. Lymphocyte- and macrophage-mediated inflammation in the lung. In: Fishman AP, Elias JA, Fishman JA, et al, eds. *Fishman's Pulmonary Diseases and Disorders*. 4th ed. New York: McGraw-Hill; 2008:291-305.
13. MacNee W, Selby C. Neutrophil kinetics in the lungs. *Clin Sci (Lond)*. 1990;79:97-107.
14. Reynolds HY. Advances in understanding pulmonary host defense mechanisms: dendritic cell function and immunomodulation. *Curr Opin Pulm Med*. 2000;6:209-216.
15. Prince AS, Mizgerd JP, Wiener-Kronish J, et al. Cell signaling underlying the pathophysiology of pneumonia. *Am J Physiol Lung Cell Mol Physiol*. 2006;291:L297-L300.
16. Strieter RM, Standiford TJ, Huffnagle GB, et al. "The good, the bad, and the ugly." The role of chemokines in models of human disease. *J Immunol*. 1996;156:3583-3586.
17. Chaudhuri N, Whyte MK, Sabroe I. Reducing the toll of inflammatory lung disease. *Chest*. 2007;131:1550-1556.
18. Puren AJ, Feldman C, Savage N, et al. Patterns of cytokine expression in community-acquired pneumonia. *Chest*. 1995;107:1342-1349.
19. Strieter RM, Belperio JA, Keane MP. Host innate defenses in the lung: the role of cytokines. *Curr Opin Infect Dis*. 2003;16:193-198.
20. Mizgerd JP. Acute lower respiratory tract infection. *N Engl J Med*. 2008;358:716-727.
21. Diamond G, Legarda D, Ryan LK. The innate immune response of the respiratory epithelium. *Immunol Rev*. 2000;173:27-38.
22. Huxley EJ, Viroslav J, Gray WR, et al. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med*. 1978;64:564-568.
23. Green GM, Carolin D. The depressant effect of cigarette smoke on the in vitro antibacterial activity of alveolar macrophages. *N Engl J Med*. 1967;276:421-427.
24. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol*. 2002;2:372-377.
25. MacGregor RR. Alcohol and immune defense. *JAMA*. 1986;256:1474-1479.
26. Schopf RE, Trompeter M, Bork K, et al. Effects of ethanol and acetaldehyde on phagocytic functions. *Arch Dermatol Res*. 1985;277:131-137.
27. Zhang P, Bagby GJ, Happel KI, et al. Pulmonary host defenses and alcohol. *Front Biosci*. 2002;7:d1314-d1330.
28. Nelson S, Mason CM, Kolls J, et al. Pathophysiology of pneumonia. *Clin Chest Med*. 1995;16:1-12.
29. Warshauer D, Goldstein E, Akers T, et al. Effect of influenza viral infection on the ingestion and killing of bacteria by alveolar macrophages. *Am Rev Respir Dis*. 1977;115:269-277.
30. Nelson S, Chidiac C, Bagby G, Summer WR. Endotoxin-induced suppression of lung host defenses. *J Med*. 1990;21:85-103.
31. Phair J, Palella FJ Jr. Host impairments associated with human immunodeficiency virus infection. In: Niederman MS, Sarosi GA, Glassroth J, eds. *Respiratory Infections*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:59-66.
32. Mason CM. The pathogenesis and presentation of nosocomial pneumonia. *Crit Care Rev*. 1991;2:145-155.
33. Nelson S, Summer WR, Jakab GJ. Aminophylline-induced suppression of pulmonary antibacterial defenses. *Am Rev Respir Dis*. 1985;131:923-927.
34. Esposito AL. Aspirin impairs antibacterial mechanisms in experimental pneumococcal pneumonia. *Am Rev Respir Dis*. 1984;130:857-862.
35. Spyridaki A, Raftogiannis M, Antonopoulou A, et al. Effect of clarithromycin in inflammatory markers of patients with ventilator-associated pneumonia and sepsis caused by gram-negative bacteria: results from a randomized clinical study. *Antimicrob Agents Chemother*. 2012;56:3819-3825.
36. Herzig SJ, Howell MD, Ngo LH, et al. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301:2120-2128.
37. Sultan N, Nazareno J, Gregor J. Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. *Can J Gastroenterol*. 2008;22:761-766.
38. Trifiro G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med*. 2010;152:418-425.
39. Ehrlich R, Henry MC. Chronic toxicity of nitrogen dioxide, I. Effect on resistance to bacterial pneumonia. *Arch Environ Health*. 1968;17:860-865.
40. Huber GL, LaForce FM, Mason RJ, et al. Impairment of pulmonary bacterial defense mechanisms by immunosuppressive agents. *Surg Forum*. 1970;21:285-286.
41. LaForce FM, Mullane JF, Boehme RF, et al. The effect of pulmonary edema on antibacterial defenses of the lung. *J Lab Clin Med*. 1973;82:634-648.
42. Perbet S, Mongardon N, Dumas F, et al. Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. *Am J Respir Crit Care Med*. 2011;184:1048-1054.
43. Gyetko MR, Toews GB. Immunology of the aging lung. *Clin Chest Med*. 1993;14:379-391.
44. Meyer KC, Ershler W, Rosenthal NS, et al. Immune dysregulation in the aging human lung. *Am J Respir Crit Care Med*. 1996;153:1072-1079.
45. Geppert EF. Chronic and recurrent pneumonia. *Semin Respir Infect*. 1992;7:282-288.
46. Beck CS, Heiner DC. Selective immunoglobulin G4 deficiency and recurrent infections of the respiratory tract. *Am Rev Respir Dis*. 1981;124:94-96.
47. Donabedian H, Gallin JI. The hyperimmunoglobulin E recurrent-infection (Job's) syndrome: a review of the NIH experience and the literature. *Medicine (Baltimore)*. 1983;62:195-208.
48. Heffelfinger JD, Davis TE, Gebrian B, et al. Evaluation of children with recurrent pneumonia diagnosed by World Health Organization criteria. *Pediatr Infect Dis J*. 2002;21:108-112.
49. Owayed AF, Campbell DM, Wang EE. Underlying causes of recurrent pneumonia in children. *Arch Pediatr Adolesc Med*. 2000;154:190-194.
50. Leigh MW, Pittman JE, Carson JL, et al. Clinical and genetic aspects of primary ciliary dyskinesia/Kartagener syndrome. *Genet Med*. 2009;11:473-487.
51. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med*. 2003;168:918-951.
52. Metlay JP, Stafford RS, Singer DE. National trends in the use of antibiotics by primary care physicians for adult patients with cough. *Arch Intern Med*. 1998;158:1813-1818.
53. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA*. 1997;278:1440-1445.
54. Metlay JP, Schulz R, Li YH, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med*. 1997;157:1453-1459.
55. Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med*. 1997;157:1709-1718.
56. Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. *JAMA*. 2013;309:275-282.
57. Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet*. 2002;359:753-759.
58. Monaco M, Antonucci R, Palange P, et al. Methicillin-resistant *Staphylococcus aureus* necrotizing pneumonia. *Emerg Infect Dis*. 2005;11:1647-1648.
59. Dorff GJ, Rytel MW, Farmer SG, et al. Etiologies and characteristic features of pneumonias in a municipal hospital. *Am J Med Sci*. 1973;266:349-358.
60. Almirall J, Bolibar I, Serra-Prat M, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J*. 2008;31:1274-1284.
61. Templeton KE, Scheltinga SA, van den Eeden WC, et al. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*. 2005;41:345-351.
62. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. *Scand J Infect Dis*. 2011;43:609-615.
63. Griffith DE, Mazurek GH. Pneumonia in chronic obstructive lung disease. *Infect Dis Clin North Am*. 1991;5:467-484.
64. Torres A, Dorca J, Zalacain R, et al. Community-acquired pneumonia in chronic obstructive pulmonary disease: a Spanish multicenter study. *Am J Respir Crit Care Med*. 1996;154:1456-1461.
65. Arancibia F, Bauer TT, Ewig S, et al. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa:* incidence, risk, and prognosis. *Arch Intern Med*. 2002;162:1849-1858.
66. Wallace JM, Rao AV, Glassroth J, et al. Respiratory illness in persons with human immunodeficiency virus infection. The Pulmonary Complications of HIV Infection Study Group. *Am Rev Respir Dis*. 1993;148(6 pt 1):1523-1529.
67. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis*. 2008;47:1345-1353.
68. Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. *Chest*. 2008;134:1287-1298.
69. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medical Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed May 7, 2013.
70. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. 2006;43:90-98.
71. Buchacz K, Baker RK, Palella FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS*. 2010;24:1549-1559.
72. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. 1995;333:845-851.
73. Hanson DL, Chu SY, Farizo KM, et al. Distribution of $CD4^+$ T lymphocytes at diagnosis of acquired immunodeficiency syndrome–defining and other human immunodeficiency virus–related illnesses. The Adult and Adolescent Spectrum of HIV Disease Project Group. *Arch Intern Med*. 1995;155:1537-1542.
74. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010;51(suppl 1):S81-S87.
75. Marrie TJ, Haldane EV, Faulkner RS, et al. Community-acquired pneumonia requiring hospitalization. Is it different in the elderly? *J Am Geriatr Soc*. 1985;33:671-680.
76. Fernandez-Sabe N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. *Medicine (Baltimore)*. 2003;82:159-169.
77. American Thoracic Society, 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*. 2005;171:388-416.
78. Carratala J, Mykietiuk A, Fernandez-Sabe N, et al. Health care–associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med*. 2007;167:1393-1399.
79. Bartlett JG, Finegold SM. Anaerobic infections of the lung and pleural space. *Am Rev Respir Dis*. 1974;110:56-77.
80. Woodhead M. Management of pneumonia in the outpatient setting. *Semin Respir Infect*. 1998;13:8-16.
81. Wipf JE, Lipsky BA, Hirschmann JV, et al. Diagnosing pneumonia by physical examination: relevant or relic? *Arch Intern Med*. 1999;159:1082-1087.
82. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. *Thorax*. 2005;60:672-678.
83. Johansson N, Kalin M, Tiveljung-Lindell A, et al. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis*. 2010;50:202-209.
84. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S72.
85. Roson B, Carratala J, Verdaguer R, et al. Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. *Clin Infect Dis*. 2000;31:869-874.

86. Miyashita N, Shimizu H, Ouchi K, et al. Assessment of the usefulness of sputum Gram stain and culture for diagnosis of community-acquired pneumonia requiring hospitalization. *Med Sci Monit*. 2008;14:CR171-CR176.
87. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis*. 2004;39:165-169.
88. Bartlett JG. Decline in microbial studies for patients with pulmonary infections. *Clin Infect Dis*. 2004;39:170-172.
89. Reimer LG, Carroll KC. Role of the microbiology laboratory in the diagnosis of lower respiratory tract infections. *Clin Infect Dis*. 1998;26:742-748.
90. George RB, Ziskind MM, Rasch JR, et al. *Mycoplasma* and adenovirus pneumonias: comparison with other atypical pneumonias in a military population. *Ann Intern Med*. 1966;65:931-942.
91. Reimann H. *The Pneumonias*. Philadelphia: Saunders; 1938.
92. Solomon S. Primary Friedlander pneumonia. *JAMA*. 1937; 108:937-947.
93. Wong LK, Barry AL, Horgan SM. Comparison of six different criteria for judging the acceptability of sputum specimens. *J Clin Microbiol*. 1982;16:627-631.
94. Rein MF, Gwaltney JM Jr, O'Brien WM, et al. Accuracy of Gram's stain in identifying pneumococci in sputum. *JAMA*. 1978;239:2671-2673.
95. Hendley JO, Sande MA, Stewart PM, et al. Spread of *Streptococcus pneumoniae* in families, I. Carriage rates and distribution of types. *J Infect Dis*. 1975;132:55-61.
96. Wallace RJ Jr, Musher DM, Martin RR. *Hemophilus influenzae* pneumonia in adults. *Am J Med*. 1978;64:87-93.
97. Levin DC, Schwarz MI, Matthay RA, et al. Bacteremic *Hemophilus influenzae* pneumonia in adults: a report of 24 cases and a review of the literature. *Am J Med*. 1977;62: 219-224.
98. Davidson M, Tempest B, Palmer DL. Bacteriologic diagnosis of acute pneumonia: comparison of sputum, transtracheal aspirates, and lung aspirates. *JAMA*. 1976;235: 158-163.
99. Murdoch DR. Diagnosis of *Legionella* infection. *Clin Infect Dis*. 2003;36:64-69.
100. Shelhamer JH, Gill VJ, Quinn TC, et al. The laboratory evaluation of opportunistic pulmonary infections. *Ann Intern Med*. 1996;124:585-599.
101. Bollee G, Sarfati C, Thiery G, et al. Clinical picture of *Pneumocystis jiroveci* pneumonia in cancer patients. *Chest*. 2007;132:1305-1310.
102. Murdoch DR. Molecular genetic methods in the diagnosis of lower respiratory tract infections. *APMIS*. 2004;112: 713-727.
103. Mahony JB. Detection of respiratory viruses by molecular methods. *Clin Microbiol Rev*. 2008;21:716-747.
104. Diederen BM, Van Der Eerden MM, Vlaspolder F, et al. Detection of respiratory viruses and *Legionella* spp. by real-time polymerase chain reaction in patients with community acquired pneumonia. *Scand J Infect Dis*. 2009;41: 45-50.
105. Baselski VS, Wunderink RG. Bronchoscopic diagnosis of pneumonia. *Clin Microbiol Rev*. 1994;7:533-558.
106. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis*. 2005;24: 241-249.
107. Chastre J, Fagon JY, Bornet-Lecso M, et al. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*. 1995;152:231-240.
108. Broughton WA, Middleton RM 3rd, Kirkpatrick MB, et al. Bronchoscopic protected specimen brush and bronchoalveolar lavage in the diagnosis of bacterial pneumonia. *Infect Dis Clin North Am*. 1991;5:437-452.
109. Marquette CH, Copin MC, Wallet F, et al. Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am J Respir Crit Care Med*. 1995;151: 1878-1888.
110. Michaud S, Suzuki S, Harbarth S. Effect of design-related bias in studies of diagnostic tests for ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;166: 1320-1325.
111. Broaddus C, Dake MD, Stulbarg MS, et al. Bronchoalveolar lavage and transbronchial biopsy for the diagnosis of pulmonary infections in the acquired immunodeficiency syndrome. *Ann Intern Med*. 1985;102:747-752.
112. Pisani RJ, Wright AJ. Clinical utility of bronchoalveolar lavage in immunocompromised hosts. *Mayo Clin Proc*. 1992;67:221-227.
113. Baughman RP, Dohn MN, Loudon RG, et al. Bronchoscopy with bronchoalveolar lavage in tuberculosis and fungal infections. *Chest*. 1991;99:92-97.
114. Avni T, Levy I, Sprecher H, et al. Diagnostic accuracy of PCR alone compared to galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis: a systematic review. *J Clin Microbiol*. 2012;50: 3652-3658.
115. Baughman R. Use of bronchoscopy in the diagnosis of infection in the immunocompromised host. *Thorax*. 1994; 49:3-7.
116. Prechter GC, Prakash UB. Bronchoscopy in the diagnosis of pulmonary histoplasmosis. *Chest*. 1989;95:1033-1036.
117. Gerbeaux P, Ledoray V, Boussuges A, et al. Diagnosis of nosocomial pneumonia in mechanically ventilated patients: repeatability of the bronchoalveolar lavage. *Am J Respir Crit Care Med*. 1998;157:76-80.
118. Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med*. 2006;355:2619-2630.
119. el-Ebiary M, Torres A, Gonzalez J, et al. Quantitative cultures of endotracheal aspirates for the diagnosis of ventilator-associated pneumonia. *Am Rev Respir Dis*. 1993; 148(6 pt 1):1552-1557.
120. Jourdain B, Novara A, Joly-Guillou ML, et al. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*. 1995;152:241-246.
121. Bregeon F, Papazian L, Visconti A, et al. Relationship of microbiologic diagnostic criteria to morbidity and mortality in patients with ventilator-associated pneumonia. *JAMA*. 1997;277:655-662.
122. Rea-Neto A, Youssef NC, Tuche F, et al. Diagnosis of ventilator-associated pneumonia: a systematic review of the literature. *Crit Care*. 2008;12:R56.
123. Torres A, Jimenez P, Puig de la Bellacasa J, et al. Diagnostic value of nonfluoroscopic percutaneous lung needle aspiration in patients with pneumonia. *Chest*. 1990;98:840-844.
124. Falguera M, Nogues A, Ruiz-Gonzalez A, et al. Transthoracic needle aspiration in the study of pulmonary infections in patients with HIV. *Chest*. 1994;106:697-702.
125. Hsu JL, Kuschner WG, Paik J, et al. The diagnostic yield of CT-guided percutaneous lung biopsy in solid organ transplant recipients. *Clin Transplant*. 2012;26:615-621.
126. Cockerill FR 3rd, Wilson WR, Carpenter HA, et al. Open lung biopsy in immunocompromised patients. *Arch Intern Med*. 1985;145:1398-1404.
127. Kramer MR, Berkman N, Mintz B, et al. The role of open lung biopsy in the management and outcome of patients with diffuse lung disease. *Ann Thorac Surg*. 1998;65: 198-202.
128. Light RW. Parapneumonic effusions and empyema. *Proc Am Thorac Soc*. 2006;3:75-80.
129. Lisboa T, Waterer GW, Lee YC. Pleural infection: changing bacteriology and its implications. *Respirology*. 2011;16: 598-603.
130. Li ST, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. *Pediatrics*. 2010;125:26-33.
131. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. *Clin Infect Dis*. 2007;45: 1480-1486.
132. Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med*. 2005;352:865-874.
133. Blaschke AJ, Heyrend C, Byington CL, et al. Molecular analysis improves pathogen identification and epidemiologic study of pediatric parapneumonic empyema. *Pediatr Infect Dis J*. 2011;30:289-294.
134. Nagesh BS, Sehgal S, Jindal SK, et al. Evaluation of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in pleural fluid. *Chest*. 2001;119:1737-1741.
135. Greco S, Girardi E, Masciangelo R, et al. Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculous pleurisy: a meta-analysis. *Int J Tuberc Lung Dis*. 2003;7:777-786.
136. Liang QL, Shi HZ, Wang K, et al. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. *Respir Med*. 2008;102:744-754.
137. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. *Respir Med*. 2001;95:78-82.
138. Metersky ML, Ma A, Bratzler DW, et al. Predicting bacteremia in patients with community-acquired pneumonia. *Am J Respir Crit Care Med*. 2004;169:342-347.
139. Falguera M, Trujillano J, Caro S, et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. *Clin Infect Dis*. 2009;49: 409-416.
140. Bordon J, Peyrani P, Brock GN, et al. The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. *Chest*. 2008;133: 618-624.
141. Campbell SG, Marrie TJ, Anstey R, et al. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective observational study. *Chest*. 2003;123:1142-1150.
142. Dedier J, Singer DE, Chang Y, et al. Processes of care, illness severity, and outcomes in the management of community-acquired pneumonia at academic hospitals. *Arch Intern Med*. 2001;161:2099-2104.
143. Berk SL. Justifying the use of blood cultures when diagnosing community-acquired pneumonia. *Chest*. 1995;108: 891-892.
144. Craven DE. Blood cultures for community-acquired pneumonia: piecing together a mosaic for doing less. *Am J Respir Crit Care Med*. 2004;169:327-328.
145. Dowell SF, Peeling RW, Boman J, et al. Standardizing *Chlamydia pneumoniae* assays: recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). *Clin Infect Dis*. 2001;33:492-503.
146. Miyashita N, Ouchi K, Kawasaki K, et al. Comparison of serological tests for detection of immunoglobulin M antibodies to *Chlamydophila pneumoniae*. *Respirology*. 2008;13: 427-431.
147. Waites KB, Talkington DF. *Mycoplasma pneumoniae* and its role as a human pathogen. *Clin Microbiol Rev*. 2004;17: 697-728.
148. Sillis M. The limitations of IgM assays in the serological diagnosis of *Mycoplasma pneumoniae* infections. *J Med Microbiol*. 1990;33:253-258.
149. Hvidsten D, Halvorsen DS, Berdal BP, et al. *Chlamydophila pneumoniae* diagnostics: importance of methodology in relation to timing of sampling. *Clin Microbiol Infect*. 2009; 15:42-49.
150. Venkatesan P, Macfarlane JT. Role of pneumococcal antigen in the diagnosis of pneumococcal pneumonia. *Thorax*. 1992;47:329-331.
151. Kee C, Palladino S, Kay I, et al. Feasibility of real-time polymerase chain reaction in whole blood to identify *Streptococcus pneumoniae* in patients with community-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2008;61:72-75.
152. Smith JA, Kauffman CA. Pulmonary fungal infections. *Respirology*. 2012;17:913-926.
153. Pickering JW, Sant HW, Bowles CA, et al. Evaluation of a (1→3)-beta-D-glucan assay for diagnosis of invasive fungal infections. *J Clin Microbiol*. 2005;43:5957-5962.
154. Onishi A, Sugiyama D, Kogata Y, et al. Diagnostic accuracy of serum 1,3-beta-D-glucan for *Pneumocystis jiroveci* pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. *J Clin Microbiol*. 2012;50:7-15.
155. Thompson GR 3rd, Bays DJ, Johnson SM, et al. Serum (1→3)-beta-D-glucan measurement in coccidioidomycosis. *J Clin Microbiol*. 2012;50:3060-3062.
156. Sax PE, Komarow L, Finkelman MA, et al. Blood (1→3)-beta-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. *Clin Infect Dis*. 2011; 53:197-202.
157. Niederman MS. Biological markers to determine eligibility in trials for community-acquired pneumonia: a focus on procalcitonin. *Clin Infect Dis*. 2008;47(suppl 3):S127-S132.
158. Christ-Crain M, Muller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J*. 2007;30: 556-573.
159. Povoa P. Serum markers in community-acquired pneumonia and ventilator-associated pneumonia. *Curr Opin Infect Dis*. 2008;21:157-162.
160. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med*. 2008;121:219-225.
161. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA*. 2009;302: 1059-1066.
162. Albrich WC, Dusemund F, Bucher B, et al. Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter poststudy survey (ProREAL). *Arch Intern Med*. 2012;172:715-722.
163. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2012;(9):CD007498.
164. Jensen JU, Heslet L, Jensen TH, et al. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med*. 2006;34:2596-2602.
165. Salluh JI, Bozza FA, Soares M, et al. Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity. *Chest*. 2008;134:947-954.
166. Christ-Crain M, Stolz D, Jutla S, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med*. 2007; 176:913-920.
167. Dominguez J, Gali N, Blanco S, et al. Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. *Chest*. 2001;119:243-249.
168. Roson B, Fernandez-Sabe N, Carratala J, et al. Contribution of a urinary antigen assay (Binax NOW) to the early

diagnosis of pneumococcal pneumonia. *Clin Infect Dis*. 2004;38:222-226.

169. Ishida T, Hashimoto T, Arita M, et al. A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology. *J Infect Chemother*. 2004;10:359-363.
170. Marcos MA, Jimenez de Anta MT, de la Bellacasa JP, et al. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. *Eur Respir J*. 2003;21:209-214.
171. Dowell SF, Garman RL, Liu G, et al. Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among pediatric patients. *Clin Infect Dis*. 2001;32:824-825.
172. Engel MF, van Velzen M, Hoepelman AI, et al. Positive urinary antigen tests for *Streptococcus pneumoniae* in community-acquired pneumonia: a 7-year retrospective evaluation of health care cost and treatment consequences. *Eur J Clin Microbiol Infect Dis*. 2013;32:485-492.
173. Albaum MN, Hill LC, Murphy M, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. *Chest*. 1996;110:343-350.
174. Boersma WG, Daniels JM, Lowenberg A, et al. Reliability of radiographic findings and the relation to etiologic agents in community-acquired pneumonia. *Respir Med*. 2006;100:926-932.
175. Rubinstein E, Kollef MH, Nathwani D. Pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2008;46(suppl 5):S378-S385.
176. Gillet Y, Vanhems P, Lina G, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. *Clin Infect Dis*. 2007;45:315-321.
177. Kim EA, Lee KS, Primack SL, et al. Viral pneumonias in adults: radiologic and pathologic findings. *RadioGraphics*. 2002;22(spec no):S137-S149.
178. Boroja M, Barrie JR, Raymond GS. Radiographic findings in 20 patients with hantavirus pulmonary syndrome correlated with clinical outcome. *AJR Am J Roentgenol*. 2002;178:159-163.
179. Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med*. 2003;348:1995-2005.
180. Wong KT, Antonio GE, Hui DS, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. *Radiology*. 2003;228:401-406.
181. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367:1814-1820.
182. Johnstone J, Majumdar SR, Fox JD, et al. Human metapneumovirus pneumonia in adults: results of a prospective study. *Clin Infect Dis*. 2008;46:571-574.
183. Hamelin ME, Cote S, Laforge J, et al. Human metapneumovirus infection in adults with community-acquired pneumonia and exacerbation of chronic obstructive pulmonary disease. *Clin Infect Dis*. 2005;41:498-502.
184. Jartti T, Hedman K, Jartti L, et al. Human bocavirus—the first 5 years. *Rev Med Virol*. 2012;22:46-64.
185. Hsieh SC, Kuo YT, Chern MS, et al. *Mycoplasma* pneumonia: clinical and radiographic features in 39 children. *Pediatr Int*. 2007;49:363-367.
186. Fine NL, Smith LR, Sheedy PF. Frequency of pleural effusions in *Mycoplasma* and viral pneumonias. *N Engl J Med*. 1970;283:790-793.
187. Fraser DW, Tsai TR, Orenstein W, et al. Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med*. 1977;297:1189-1197.
188. Pope TL Jr, Armstrong P, Thompson R, et al. Pittsburgh pneumonia agent: chest film manifestations. *AJR Am J Roentgenol*. 1982;138:237-241.
189. Syrjala H, Broas M, Suramo I, et al. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clin Infect Dis*. 1998;27:358-363.
190. Hayden GE, Wrenn KW. Chest radiograph vs. computed tomography scan in the evaluation for pneumonia. *J Emerg Med*. 2009;36:266-270.
191. Reynolds JH, McDonald G, Alton H, et al. Pneumonia in the immunocompetent patient. *Br J Radiol*. 2010;83:998-1009.
192. Love C, Palestro CJ. Radionuclide imaging of inflammation and infection in the acute care setting. *Semin Nucl Med*. 2013;43:102-113.
193. Marrie TJ, Peeling RW, Fine MJ, et al. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. *Am J Med*. 1996;101:508-515.
194. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. *Medicine (Baltimore)*. 1990;69:307-316.
195. Centers for Disease Control and Prevention. Legionellosis—United States, 2000-2009. *MMWR Morb Mortal Wkly Rep*. 2011;60:1083-1086.
196. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med*. 1995;152(4 pt 1):1309-1315.
197. Bochud PY, Moser F, Erard P, et al. Community-acquired pneumonia: a prospective outpatient study. *Medicine (Baltimore)*. 2001;80:75-87.
198. Halm EA, Teirstein AS. Clinical practice. Management of community-acquired pneumonia. *N Engl J Med*. 2002;347:2039-2045.
199. Fine MJ, Stone RA, Singer DE, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med*. 1999;159:970-980.
200. Metlay JP, Fine MJ, Schulz R, et al. Measuring symptomatic and functional recovery in patients with community-acquired pneumonia. *J Gen Intern Med*. 1997;12:423-430.
201. Marrie TJ, Poulin-Costello M, Beecroft MD, et al. Etiology of community-acquired pneumonia treated in an ambulatory setting. *Respir Med*. 2005;99:60-65.
202. Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. *Thorax*. 2001;56:296-301.
203. File TM. Community-acquired pneumonia. *Lancet*. 2003;362:1991-2001.
204. Albrich WC, Baughman W, Schmotzer B, et al. Changing characteristics of invasive pneumococcal disease in Metropolitan Atlanta, Georgia, after introduction of a 7-valent pneumococcal conjugate vaccine. *Clin Infect Dis*. 2007;44:1569-1576.
205. Griffin MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369:155-163.
206. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet*. 2011;378:86-97.
207. Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: a 14-year experience in an inner-city university hospital. *Clin Infect Dis*. 1995;21:345-351.
208. Dworkin MS, Park L, Borchardt SM. The changing epidemiology of invasive *Haemophilus influenzae* disease, especially in persons > or =65 years old. *Clin Infect Dis*. 2007;44:810-816.
209. Mathew J, Addai T, Anand A, et al. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. *Arch Intern Med*. 1995;155:1641-1648.
210. Naraqi S, McDonnell G. Hematogenous staphylococcal pneumonia secondary to soft tissue infection. *Chest*. 1981;79:173-175.
211. Gillet Y, Etienne J, Lina G, et al. Association of necrotizing pneumonia with Panton-Valentine leukocidin-producing *Staphylococcus aureus*, regardless of methicillin resistance. *Clin Infect Dis*. 2008;47:985-986.
212. Kang CI, Song JH, Oh WS, et al. Clinical outcomes and risk factors of community-acquired pneumonia caused by gram-negative bacilli. *Eur J Clin Microbiol Infect Dis*. 2008;27:657-661.
213. Yu VL, Kroboth FJ, Shonnard J, et al. Legionnaires' disease: new clinical perspective from a prospective pneumonia study. *Am J Med*. 1982;73:357-361.
214. Neil K, Berkelman R. Increasing incidence of legionellosis in the United States, 1990-2005: changing epidemiologic trends. *Clin Infect Dis*. 2008;47:591-599.
215. Nicotra B, Rivera M, Luman JI, et al. *Branhamella catarrhalis* as a lower respiratory tract pathogen in patients with chronic lung disease. *Arch Intern Med*. 1986;146:890-893.
216. Donowitz GR, Cox HL. Bacterial community-acquired pneumonia in older patients. *Clin Geriatr Med*. 2007;23:515-534.
217. Koivula I, Sten M, Makela PH. Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Arch Intern Med*. 1999;159:1550-1555.
218. Johnson JC, Jayadevappa R, Baccash PD, et al. Nonspecific presentation of pneumonia in hospitalized older people: age effect or dementia? *J Am Geriatr Soc*. 2000;48:1316-1320.
219. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Ann Intern Med*. 1964;60:759-776.
220. Berk SL, Holtsclaw SA, Wiener SL, et al. Nontypeable *Haemophilus influenzae* in the elderly. *Arch Intern Med*. 1982;142:537-539.
221. Valenti WM, Trudell RG, Bentley DW. Factors predisposing to oropharyngeal colonization with gram-negative bacilli in the aged. *N Engl J Med*. 1978;298:1108-1111.
222. El-Solh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med*. 2003;167:1650-1654.
223. Maruyama T, Niederman MS, Kobayashi T, et al. A prospective comparison of nursing home-acquired pneumonia with hospital-acquired pneumonia in non-intubated elderly. *Respir Med*. 2008;102:1287-1295.
224. Falsey AR, Walsh EE. Viral pneumonia in older adults. *Clin Infect Dis*. 2006;42:518-524.
225. Johnstone J, Majumdar SR, Fox JD, et al. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest*. 2008;134:1141-1148.
226. Jennings LC, Anderson TP, Beynon KA, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax*. 2008;63:42-48.
227. Ishizuka S, Yamaya M, Suzuki T, et al. Effects of rhinovirus infection on the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells. *J Infect Dis*. 2003;188:1928-1939.
228. Mylotte JM. Nursing home-acquired pneumonia. *Clin Infect Dis*. 2002;35:1205-1211.
229. Chan Carusone SB, Walter SD, Brazil K, et al. Pneumonia and lower respiratory infections in nursing home residents: predictors of hospitalization and mortality. *J Am Geriatr Soc*. 2007;55:414-419.
230. Mylotte JM. Nursing home-associated pneumonia. *Clin Geriatr Med*. 2007;23:553-565.
231. Quagliarello V, Ginter S, Han L, et al. Modifiable risk factors for nursing home-acquired pneumonia. *Clin Infect Dis*. 2005;40:1-6.
232. Hicks LA, Shepard CW, Britz PH, et al. Two outbreaks of severe respiratory disease in nursing homes associated with rhinovirus. *J Am Geriatr Soc*. 2006;54:284-289.
233. Strausbaugh LJ, Sukumar SR, Joseph CL. Infectious disease outbreaks in nursing homes: an unappreciated hazard for frail elderly persons. *Clin Infect Dis*. 2003;36:870-876.
234. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243-250.
235. Pachon J, Prados MD, Capote F, et al. Severe community-acquired pneumonia: etiology, prognosis, and treatment. *Am Rev Respir Dis*. 1990;142:369-373.
236. Rello J, Quintana E, Ausina V, et al. A three-year study of severe community-acquired pneumonia with emphasis on outcome. *Chest*. 1993;103:232-235.
237. Matsumura Y, Shindo Y, Iinuma Y, et al. Clinical characteristics of *Pneumocystis* pneumonia in non-HIV patients and prognostic factors including microbiological genotypes. *BMC Infect Dis*. 2011;11:76.
238. Monnet X, Vidal-Petiot E, Osman D, et al. Critical care management and outcome of severe *Pneumocystis* pneumonia in patients with and without HIV infection. *Crit Care*. 2008;12:R28.
239. Martin-Garrido I, Carmona EM, Specks U, et al. *Pneumocystis* pneumonia in patients treated with rituximab. *Chest*. 2013;144:258-265.
240. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA*. 1996;275:134-141.
241. Neill AM, Martin IR, Weir R, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax*. 1996;51:1010-1016.
242. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377-382.
243. Capelastegui A, Espana PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J*. 2006;27:151-157.
244. Espana PP, Capelastegui A, Gorordo I, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med*. 2006;174:1249-1256.
245. Charles PG, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis*. 2008;47:375-384.
246. Labarere J, Schuetz P, Renaud B, et al. Validation of a clinical prediction model for early admission to the intensive care unit of patients with pneumonia. *Acad Emerg Med*. 2012;19:993-1003.
247. Venditti M, Falcone M, Corrao S, et al; Study Group of the Italian Society of Internal Medicine. Outcomes of patients hospitalized with community-acquired, health care-associated, and hospital-acquired pneumonia. *Ann Intern Med*. 2009;150:19-26.
248. Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;128:3854-3862.
249. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia: a disease entity probably caused by a filtrable virus. *JAMA*. 1938;111:2377-2384.
250. Hohenthal U, Vainionpaa R, Meurman O, et al. Aetiological diagnosis of community acquired pneumonia: utility of rapid microbiological methods with respect to disease severity. *Scand J Infect Dis*. 2008;40:131-138.
251. Falguera M, Sacristan O, Nogues A, et al. Nonsevere community-acquired pneumonia: correlation between

cause and severity or comorbidity. *Arch Intern Med*. 2001; 161:1866-1872.

252. Ruiz-Gonzalez A, Falguera M, Nogues A, et al. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *Am J Med*. 1999;106:385-390.
253. Miyashita N, Ouchi K, Kawasaki K, et al. *Mycoplasma pneumoniae* pneumonia in the elderly. *Med Sci Monit*. 2008;14:CR387-CR391.
254. Miyashita N, Obase Y, Ouchi K, et al. Clinical features of severe *Mycoplasma pneumoniae* pneumonia in adults admitted to an intensive care unit. *J Med Microbiol*. 2007;56(pt 12):1625-1629.
255. File TM Jr, Plouffe JF Jr, Breiman RF, et al. Clinical characteristics of *Chlamydia pneumoniae* infection as the sole cause of community-acquired pneumonia. *Clin Infect Dis*. 1999;29:426-428.
256. Grayston JT. Infections caused by *Chlamydia pneumoniae* strain TWAR. *Clin Infect Dis*. 1992;15:757-761.
257. Falsey AR, Cunningham CK, Barker WH, et al. Respiratory syncytial virus and influenza A infections in the hospitalized elderly. *J Infect Dis*. 1995;172:389-394.
258. Lieberman D, Shimoni A, Shemer-Avni Y, et al. Respiratory viruses in adults with community-acquired pneumonia. *Chest*. 2010;138:811-816.
259. Garcia-Garcia ML, Calvo C, Pozo F, et al. Spectrum of respiratory viruses in children with community-acquired pneumonia. *Pediatr Infect Dis J*. 2012;31:808-813.
260. Choi SH, Hong SB, Ko GB, et al. Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med*. 2012;186:325-332.
261. Pretorius MA, Madhi SA, Cohen C, et al. Respiratory viral coinfections identified by a 10-plex real-time reverse-transcription polymerase chain reaction assay in patients hospitalized with severe acute respiratory illness—South Africa, 2009-2010. *J Infect Dis*. 2012;206(suppl 1): S159-S165.
262. Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. *Lancet*. 2011;377:1264-1275.
263. Yu VL, Plouffe JF, Pastoris MC, et al. Distribution of *Legionella* species and serogroups isolated by culture in patients with sporadic community-acquired legionellosis: an international collaborative survey. *J Infect Dis*. 2002;186: 127-128.
264. Stout JE, Yu VL. Legionellosis. *N Engl J Med*. 1997;337: 682-687.
265. Reza Shariatzadeh M, Huang JQ, Marrie TJ. Differences in the features of aspiration pneumonia according to site of acquisition: community or continuing care facility. *J Am Geriatr Soc*. 2006;54:296-302.
266. Matthay MA, Rosen GD. Acid aspiration induced lung injury: new insights and therapeutic options. *Am J Respir Crit Care Med*. 1996;154(2 pt 1):277-278.
267. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344:665-671.
268. Rabinovici R, Neville LF, Abdullah F, et al. Aspiration-induced lung injury: role of complement. *Crit Care Med*. 1995;23:1405-1411.
269. Finegold SM. Aspiration pneumonia. *Rev Infect Dis*. 1991;13(suppl 9):S737-S742.
270. Bartlett JG. Anaerobic bacterial infections of the lung and pleural space. *Clin Infect Dis*. 1993;16(suppl 4):S248-S255.
271. Cottin V, Cordier JF. Eosinophilic pneumonias. *Allergy*. 2005;60:841-857.
272. Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med*. 1994;150:1423-1438.
273. Philit F, Etienne-Mastroianni B, Parrot A, et al. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. *Am J Respir Crit Care Med*. 2002;166:1235-1239.
274. Marchand E, Reynaud-Gaubert M, Lauque D, et al. Idiopathic chronic eosinophilic pneumonia: a clinical and follow-up study of 62 cases. Groupe d'Études et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore)*. 1998;77:299-312.
275. Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest*. 2009;135:805-826.
276. Barbier F, Andremont A, Wolff M, et al. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. *Curr Opin Pulm Med*. 2013;19:216-228.
277. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep*. 2004;53(RR-3):1-36.
278. Stone PW, Kunches L, Hirschhorn L. Cost of hospital-associated infections in Massachusetts. *Am J Infect Control*. 2009;37:210-214.
279. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med*. 1998;129:433-440.
280. Bonten MJ, Gaillard CA, de Leeuw PW, et al. Role of colonization of the upper intestinal tract in the pathogenesis of ventilator-associated pneumonia. *Clin Infect Dis*. 1997;24: 309-319.
281. Weber DJ, Rutala WA, Sickbert-Bennett EE, et al. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. *Infect Control Hosp Epidemiol*. 2007;28:825-831.
282. Bartlett JG, O'Keefe P, Tally FP, et al. Bacteriology of hospital-acquired pneumonia. *Arch Intern Med*. 1986;146: 868-871.
283. Dore P, Robert R, Grollier G, et al. Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. *Am J Respir Crit Care Med*. 1996;153 (4 pt 1):1292-1298.
284. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009;64(suppl 3):iii1-iii55.
285. Niederman MS, McCombs JS, Unger AN, et al. The cost of treating community-acquired pneumonia. *Clin Ther*. 1998;20:820-837.
286. Carratala J, Fernandez-Sabe N, Ortega L, et al. Outpatient care compared with hospitalization for community-acquired pneumonia: a randomized trial in low-risk patients. *Ann Intern Med*. 2005;142:165-172.
287. Coley CM, Li YH, Medsger AR, et al. Preferences for home vs hospital care among low-risk patients with community-acquired pneumonia. *Arch Intern Med*. 1996; 156:1565-1571.
288. Marrie TJ, Lau CY, Wheeler SL, et al. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA*. 2000;283:749-755.
289. Atlas SJ, Benzer TI, Borowsky LH, et al. Safely increasing the proportion of patients with community-acquired pneumonia treated as outpatients: an interventional trial. *Arch Intern Med*. 1998;158:1350-1356.
290. Chalmers JD, Singanayagam A, Akram AR, et al. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia: systematic review and meta-analysis. *Thorax*. 2010;65:878-883.
291. Chalmers JD, Akram AR, Hill AT. Increasing outpatient treatment of mild community-acquired pneumonia: systematic review and meta-analysis. *Eur Respir J*. 2011;37: 858-864.
292. Fang WF, Yang KY, Wu CL, et al. Application and comparison of scoring indices to predict outcomes in patients with healthcare-associated pneumonia. *Crit Care*. 2011;15:R32.
293. Carrabba M, Zarantonello M, Bonara P, et al. Severity assessment of healthcare-associated pneumonia and pneumonia in immunosuppression. *Eur Respir J*. 2012;40: 1201-1210.
294. Chalmers JD, Taylor JK, Mandal P, et al. Validation of the Infectious Diseases Society of America/American Thoracic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. *Clin Infect Dis*. 2011;53:503-511.
295. Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: in vivo observations and clinical relevance. *Antimicrob Agents Chemother*. 1992;36: 1176-1180.
296. Silverman JA, Mortin LI, Vanpraagh AD, et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis*. 2005;191:2149-2152.
297. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1-10.
298. Jacobs MR. Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. *Clin Microbiol Infect*. 2001;7:589-596.
299. Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am J Med*. 1984;77:657-662.
300. Kashuba AD, Nafziger AN, Drusano GL, et al. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob Agents Chemother*. 1999;43:623-629.
301. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet*. 2004;43:925-942.
302. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82-98.
303. Deresinski S. Counterpoint: Vancomycin and *Staphylococcus aureus*—an antibiotic enters obsolescence. *Clin Infect Dis*. 2007;44:1543-1548.
304. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;66 (suppl 2):ii1-ii23.
305. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53: e25-e76.
306. Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clin Infect Dis*. 2003;37:230-237.
307. Ho PL, Tse WS, Tsang KW, et al. Risk factors for acquisition of levofloxacin-resistant *Streptococcus pneumoniae:* a case-control study. *Clin Infect Dis*. 2001;32:701-707.
308. Vanderkooi OG, Low DE, Green K, et al; Toronto Invasive Bacterial Disease Network. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis*. 2005;40:1288-1297.
309. Daneman N, McGeer A, Green K, et al; Toronto Invasive Bacterial Diseases Network. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. *Clin Infect Dis*. 2006;43:432-438.
310. Daneman N, Low DE, McGeer A, et al. At the threshold: defining clinically meaningful resistance thresholds for antibiotic choice in community-acquired pneumonia. *Clin Infect Dis*. 2008;46:1131-1138.
311. Asadi L, Sligl WI, Eurich DT, et al. Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: a systematic review and meta-analysis. *Clin Infect Dis*. 2012;55:371-380.
312. Asadi L, Eurich DT, Gamble JM, et al. Guideline adherence and macrolides reduced mortality in outpatients with pneumonia. *Respir Med*. 2012;106:451-458.
313. Asadi L, Eurich DT, Gamble JM, et al. Impact of guideline-concordant antibiotics and macrolide/beta-lactam combinations in 3203 patients hospitalized with pneumonia: prospective cohort study. *Clin Microbiol Infect*. 2013;19: 257-264.
314. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012;366: 1881-1890.
315. Mosholder AD, Mathew J, Alexander JJ, et al. Cardiovascular risks with azithromycin and other antibacterial drugs. *N Engl J Med*. 2013;368:1665-1668.
316. Svanstrom H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. *N Engl J Med*. 2013;368:1704-1712.
317. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52:285-292.
318. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54:621-629.
319. Saravolatz LD, Stein GE, Johnson LB. Ceftaroline: a novel cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2011;52:1156-1163.
320. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med*. 2007;35:1888-1895.
321. Heyland DK, Dodek P, Muscedere J, et al; Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med*. 2008;36: 737-744.
322. Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother*. 2010;54: 1742-1748.
323. Rodriguez A, Mendia A, Sirvent JM, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med*. 2007;35:1493-1498.
324. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278:2080-2084.
325. Houck PM, Bratzler DW, Nsa W, et al. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2004;164:637-644.
326. Welker JA, Huston M, McCue JD. Antibiotic timing and errors in diagnosing pneumonia. *Arch Intern Med*. 2008;168:351-356.
327. Nicks BA, Manthey DE, Fitch MT. The Centers for Medicare and Medicaid Services (CMS) community-acquired pneumonia core measures lead to unnecessary antibiotic administration by emergency physicians. *Acad Emerg Med*. 2009;16:184-187.
328. Quattromani E, Powell ES, Khare RK, et al. Hospital-reported data on the pneumonia quality measure "Time to

First Antibiotic Dose" are not associated with inpatient mortality: results of a nationwide cross-sectional analysis. *Acad Emerg Med*. 2011;18:496-503.
329. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589-1596.
330. Rice LB. The Maxwell Finland Lecture: for the duration-rational antibiotic administration in an era of antimicrobial resistance and *Clostridium difficile*. *Clin Infect Dis*. 2008;46:491-496.
331. Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA*. 1998;279:1452-1457.
332. Akram AR, Chalmers JD, Taylor JK, et al. An evaluation of clinical stability criteria to predict hospital course in community-acquired pneumonia. *Clin Microbiol Infect*. 2013;19:1174-1180.
333. Hitt CM, Nightingale CH, Quintiliani R, et al. Streamlining antimicrobial therapy for lower respiratory tract infections. *Clin Infect Dis*. 1997;24(suppl 2):S231-S237.
334. Castro-Guardiola A, Viejo-Rodriguez AL, Soler-Simon S, et al. Efficacy and safety of oral and early-switch therapy for community-acquired pneumonia: a randomized controlled trial. *Am J Med*. 2001;111:367-374.
335. Oosterheert JJ, Bonten MJ, Schneider MM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ*. 2006;333:1193.
336. Nathan RV, Rhew DC, Murray C, et al. In-hospital observation after antibiotic switch in pneumonia: a national evaluation. *Am J Med*. 2006;119:512.e1-512.e7.
337. Halm EA, Fine MJ, Kapoor WN, et al. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch Intern Med*. 2002;162:1278-1284.
338. Capelastegui A, Espana Yandiola PP, Quintana JM, et al. Predictors of short-term rehospitalization following discharge of patients hospitalized with community-acquired pneumonia. *Chest*. 2009;136:1079-1085.
339. Li JZ, Winston LG, Moore DH, et al. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. *Am J Med*. 2007;120:783-790.
340. el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ*. 2006;332:1355.
341. Frei CR, Restrepo MI, Mortensen EM, et al. Impact of guideline-concordant empiric antibiotic therapy in community-acquired pneumonia. *Am J Med*. 2006;119:865-871.
342. Arnold FW, LaJoie AS, Brock GN, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. *Arch Intern Med*. 2009;169:1515-1524.
343. McCabe C, Kirchner C, Zhang H, et al. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med*. 2009;169:1525-1531.
344. Webb BJ, Dangerfield BS, Pasha JS, et al. Guideline-concordant antibiotic therapy and clinical outcomes in healthcare-associated pneumonia. *Respir Med*. 2012;106:1606-1612.
345. Fine MJ, Stone RA, Lave JR, et al. Implementation of an evidence-based guideline to reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized with community-acquired pneumonia: a randomized controlled trial. *Am J Med*. 2003;115:343-351.
346. Carratala J, Garcia-Vidal C, Ortega L, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. *Arch Intern Med*. 2012;172:922-928.
347. Jasti H, Mortensen EM, Obrosky DS, et al. Causes and risk factors for rehospitalization of patients hospitalized with community-acquired pneumonia. *Clin Infect Dis*. 2008;46:550-556.
348. Amsden GW. Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimicrob Chemother*. 2005;55:10-21.
349. Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377:2023-2030.
350. Shafiq M, Mansoor MS, Khan AA, et al. Adjuvant steroid therapy in community-acquired pneumonia: a systematic review and meta-analysis. *J Hosp Med*. 2013;8:68-75.
351. Chopra V, Flanders SA. Does statin use improve pneumonia outcomes? *Chest*. 2009;136:1381-1388.
352. Yende S, Milbrandt EB, Kellum JA, et al. Understanding the potential role of statins in pneumonia and sepsis. *Crit Care Med*. 2011;39:1871-1878.
353. Siempos II, Vardakas KZ, Kopterides P, et al. Adjunctive therapies for community-acquired pneumonia: a systematic review. *J Antimicrob Chemother*. 2008;62:661-668.
354. Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med*. 1995;123:518-527.
355. Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007;357:1373-1381.
356. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2012-13 influenza season. *MMWR Morb Mortal Wkly Rep*. 2012;61:613-618.
357. Johnstone J, Eurich DT, Minhas JK, et al. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. *Clin Infect Dis*. 2010;51:15-22.
358. Moberley S, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev*. 2013;(1):CD000422.
359. Almirall J, Bolibar I, Balanzo X, et al. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. *Eur Respir J*. 1999;13:349-355.
360. Cecere LM, Williams EC, Sun H, et al. Smoking cessation and the risk of hospitalization for pneumonia. *Respir Med*. 2012;106:1055-1062.