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67 Acute Pneumonia

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SHORT VIEW SUMMARY

Epidemiology and Etiology

- Acute pneumonia is the most common cause of infection-related death.
- Predominant pathogens of community-acquired pneumonia (CAP) in adults in the developed world include *Streptococcus pneumoniae, Mycoplasma pneumoniae,* and community respiratory viruses.
- *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 and 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.
- Analyses of sputum samples by Gram stain and culture remain valuable diagnostic assays.
- Blood cultures should be obtained in all patients who are immunocompromised, have health care–associated pneumonia (HCAP) or hospital-acquired pneumonia, or are hospitalized with severe CAP.
- Analysis of pleural fluid should be performed on all effusions with imaging characteristics atypical of fluid overload.
- Chest radiographs should be obtained in all adult patients suspected to have 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 usefulness of such assays has not yet been established.

Management

- One of three severity index scores (pneumonia severity index [PSI]; confusion, *u*rea, *r*espiratory rate, low *b*lood pressure plus age >65 [CURB-65]; or CURB-65 score without the urea level [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 67.5 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 patient's clinical response.

Prevention

- Immunization with the influenza and pneumococcal vaccines should be performed as appropriate.
- 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] Despite ongoing advances in medical care, over a century later the prominence of pneumonia as a clinical entity remains. It remained among the top 10 most common causes of death among all age groups worldwide in 2015 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 67.1A–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 constitutes inspired air. Although the lower respiratory tract has traditionally been considered sterile, investigations using culture-independent techniques have shown that in 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 (COPD), cystic fibrosis (CF), bronchiectasis, lung transplant, and altered mucociliary transport, and there can be significant variations in the microbiota at different locations within the lungs of individuals.[4–6] 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

TABLE 67.1A Causative Agents of Acute Pneumonia: Bacteria

COMMON	UNCOMMON
Streptococcus pneumoniae	*Acinetobacter* var. *anitratus*
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 67.1B 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 67.1C 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.
Blastomyces dermatitidis	*Cunninghamella* spp.
	Candida spp.

TABLE 67.1D Causative Agents of Acute Pneumonia: Other Agents

Rickettsia
Coxiella burnetii
Rickettsia rickettsiae
Mycoplasma* and *Chlamydia
Mycoplasma pneumoniae
Chlamydia psittaci
Chlamydia trachomatis
Chlamydia pneumoniae (TWAR)
Mycobacteria
Mycobacterium tuberculosis
Nontuberculous Mycobacteria
M. abscessus
M. avium 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

immunity, cell-mediated immunity, and phagocyte activity (Table 67.2).[7–9] 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.

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 larger 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 in size. 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—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.[10,11] Respiratory epithelial cells produce other potent antimicrobial peptides including cathelicidins and β-defensins.[12] These peptides possess individual antimicrobial activity and synergistic antimicrobial activity with one another. 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 in size. 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.[13] SP-A and SP-D are collectins—a family of collagenous carbohydrate-binding

TABLE 67.2 Pulmonary Host Defenses

LOCATION	HOST DEFENSE MECHANISM[a]
Upper Airways	
Nasopharynx	Nasal hair Turbinates Anatomy of upper airways Mucociliary apparatus Immunoglobulin A (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[b] } Antigen processing and presentation → stimulation of memory and effector T cells and B cells Bronchus-associated lymphoid tissue (BALT) 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[c] (pattern recognition receptors → transcription factor stimulation → proinflammatory and antiinflammatory cytokine and chemokine production) Dendritic cells[b] } Antigen processing and presentation → stimulation of memory and effector T cells and B cells Bronchus-associated lymphoid tissue (BALT)

[a]Aspects of native and adaptive immunity play a role throughout the respiratory tract.
[b]Major component of adaptive immunity and important in response to vaccines and prior infections.
[c]Major component of innate immunity.

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.[14] 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.[15,16] 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.[8] As phagocytic cells, they can eliminate certain organisms. If the numbers 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.[17] Interstitial macrophages are located in the lung connective tissue and serve both as 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.[18] 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.[19] 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.[9,20–24] Other lung parenchymal cells may also help regulate the inflammatory response.[25] 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 antiinflammatory (IL-10) factors.

Microorganisms express molecular recognition patterns that are unique and different from those of the host. Pattern recognition receptor families such as Toll-like receptors are present on epithelioid cells, alveolar macrophages, dendritic cells, and 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.[22,25] This recognition leads to the generation of early response cytokines such as tumor necrosis factor-α (TNF-α) and IL-1, which 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 antiinflammatory response mediators, which lead to the shedding of receptors, neutralization of cytokines, and inhibition of macrophage recruitment, all of which 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 proinflammatory and antiinflammatory 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 antiinflammatory mediators, and that these genetic variations can contribute to an individual's susceptibility to pneumonia.[24]

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*).[16] Lymphocytes within the lung are found along the epithelial

surfaces and within the interstitial and intravascular spaces. Lymphocytes at the epithelial surface are predominantly memory T cells and interact both with epithelial cells and with dendritic cells. Interstitial cells are similarly predominantly T cells but with a different CD4/CD8 ratio than seen in either lymphocytes at the epithelial surface or intravascular lymphocytes, and with an abundance of natural killer (NK) 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. These collections appear to be morphologically similar to Peyer 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 intraalveolar 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 1 (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, and 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 mediating immune tolerance. The lung contains a variety of cytotoxic T cells including NK 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 appear 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, several 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.[26] Cigarette smoke, perhaps the most common agent involved in compromising natural pulmonary defense mechanisms, disrupts mucociliary transport and alters macrophage and B- and T-lymphocyte functionality.[27,28]

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.[29,30] 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 antiinflammatory properties.[31]

Infections with *Mycoplasma pneumoniae* or *Haemophilus influenzae* may interfere with normal ciliary function.[32] 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.[33,34] 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.[35] 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.[36,37] 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.

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.[38,39] Data with macrolides suggest that they have immunomodulatory activity that could have beneficial effects in some settings.[40,41] 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.[42–44]

Other factors that impair pulmonary host defenses include hypoxemia, acidosis, toxic inhalations, particulate air pollutants, pulmonary edema, uremia, malnutrition, immunosuppressive agents, and mechanical obstruction.[45,46] Recent clinical studies have also shown an increased risk of pneumonia, with therapeutic hypothermia now being used for management of cardiac arrest and head trauma.[47]

Older adults are at increased risk for the development of pneumonia (see Chapter 310). 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.[48] 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.

Recurrent episodes of bacterial pneumonia suggest the presence of specific predisposing factors.[49–51] 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.[52–55] Congenital defects in ciliary activity and CF are other clinical entities associated with recurrent pneumonia in young persons.[56,57] 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.[22,24,55]

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 COPD, bronchiectasis, adult-onset CF, bronchopulmonary sequestration, and tracheobronchiomegaly may manifest with 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 or not, (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 and may have a number of infectious and noninfectious causes.[58] Clinicians need to differentiate pneumonia from other clinical entities with which it may be confused. The clinician should ask the patient about symptoms that are often associated with pneumonia including cough, sputum production, dyspnea, chest pain, and fever.[59] They should also ask if patient has hemoptysis, hoarseness, vomiting, or trouble swallowing and should inquire about recent travel, weight change, and smoking. In addition, nonrespiratory symptoms are commonly present including fatigue, sweats, headache, nausea, and myalgia, and occasionally abdominal pain and diarrhea.[60] With increasing age, both respiratory and nonrespiratory symptoms of pneumonia become less frequent. In children younger than 6 years, chest radiographs may reveal pneumonia in the absence of lung findings at physical examination.[61] Unfortunately, symptoms at presentation elucidated by a careful history may not always aid in distinguishing 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 in older patients it may be a cause of pneumonia severe enough to necessitate hospitalization.[62] Gram-negative bacterial pneumonia tends to occur in older adults, especially those who are debilitated with comorbid diseases or are ill enough to require intensive care unit (ICU) care. Tuberculosis should be suspected in persons who have lived in countries where tuberculosis is endemic, are homeless, are infected with HIV, have a history of latent tuberculosis, or have been exposed to others with the disease. Staphylococcal pneumonia classically has been noted during epidemics of influenza,[63] yet was shown to cause only 1.6% in a study of over 2000 adults in the United States with CAP, with only 0.7% of the total cohort being due to methicillin-resistant *Staphylococcus aureus* (MRSA).[64] Despite this fact, the study noted that 30% of the adults received antibacterials targeting MRSA.

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.[65] Certain lifestyle factors have also been associated with an increased risk of 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.[66] Viral upper respiratory tract infections can predispose to pneumonia, and may be associated with more severe disease.[67,68] Recent dental manipulations, sedative overdoses, seizures, alcoholism, or loss of consciousness for any reason should raise the suspicion of anaerobic infection caused by aspiration of oral contents.[26]

Special note needs to be made of the relationship between pneumonia and patients with COPD.[69] 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 a key 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 including *Moraxella catarrhalis, Legionella, Chlamydia,* and aerobic gram-negative rods including *P. aeruginosa* also play a significant role in causing disease.[69–71] Patients with CF more often have pneumonia due to *Pseudomonas* and staphylococci,[57] and *Burkholderia* spp., *Stenotrophomonas* spp., *Achromobacter xylosoxidans,* and atypical mycobacteria. Pulmonary alveolar proteinosis can be associated with *Nocardia* infection.

Patients infected with HIV are at high risk for the development of pulmonary infections.[72–75] 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. Principle 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.[73,76] In considering the etiology of pulmonary infection in patients infected with HIV, providers should consider geographic exposures, demographic characteristics of the patient, and the degree of immune suppression. With the development of highly active antiretroviral therapy and effective prophylactic strategies, the incidence of *Pneumocystis jirovecii* pneumonia in patients with AIDS has decreased to less than 1 per 100 patient-years from 70% to 80%.[77] It is now predominantly seen in individuals who have a CD4 count less than 100 per mm^3 and are either unaware of having HIV infection or are not receiving care.[75] Bacterial pneumonia was a significant complication for HIV-infected individuals in the preantiretroviral era, with an incidence 5- to 10-fold that seen in the general population, and the incidence of invasive pneumococcal disease was more than 50-fold higher in in HIV-infected patients than in non–HIV-infected controls.[76,78] The incidence of these infections has now decreased, although there remains a high risk in patients not on treatment and in those who present unaware of their HIV infection.[75,77] The incidence of pneumonia due to *P. aeruginosa* and *S. aureus* has also been notably higher in HIV-infected patients.[75] 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.[74] The use of highly active antiretroviral therapy has led to a decreased incidence of disease, but in endemic settings its overall importance as a pulmonary pathogen remains.[79] 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. *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.[80] Pulmonary infections in HIV-infected patients are discussed in more detail in Chapter 123.

Pneumonia developing in hospitalized patients may involve Enterobacteriaceae, *P. aeruginosa,* and *S. aureus,* organisms that are unusual in community-acquired disease.[81] Pneumonia in older adults, especially those who are bedridden or who have chronic diseases, had been felt to be more often associated with gram-negative bacilli than is pneumonia in younger populations, but this association remains unclear.[82,83] In general, elderly patients most frequently have infection due to *S. pneumoniae*, nontypeable strains of *H. influenzae,* or *M. catarrhalis* or aspiration pneumonia. Pneumonia is a manifestation of aging: the annual incidence of pneumonia necessitating hospital admission rises with age, and those aged 80 years or older have the highest rate (164 per 10,000 adults).[84] It has been recognized that patients with outpatient contact with the health care system develop pneumonia with etiologic

TABLE 67.3 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 worker 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 in Mississippi or Ohio river valleys, Caribbean, central America or Africa, South Asia	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 in Southeast Asia	Paragonimiasis, Melioidosis
Residence or travel to West Indies, Australia, or Guam	Melioidosis

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

agents that may be seen in both CAP and nosocomial pneumonia.[85–87] 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 67.3). A carefully obtained history may also suggest the presence of noninfectious pulmonary disease, such as tumors, sarcoidosis, granulomatosis with polyangiitis (GPA; previously known as Wegener granulomatosis), or pulmonary emboli, all of which may masquerade as pneumonia. Patients with a history of several episodes of "pneumonia" with abnormal imaging that does not resolve need to be evaluated for a noninfectious cause.

Physical Examination

Most, but not all patients with acute pneumonia appear ill, although the elderly can 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 per minute 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 or septic emboli to the lung via hematogenous spread. Bullous myringitis is an infrequent but significant finding in mycoplasmal pneumonia (was seen in volunteers given intranasal infections). 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.[88]

Examination of the thorax may reveal "splinting," or an inspiratory lag on the side of the lesion, that is suggestive of bacterial pneumonia. Deep breathing can provoke cough. Early in the disease process, definitive signs of pulmonary involvement may be lacking or may manifest only as fine rales. Chest examination may reveal these early signs of pneumonia even though the chest film is normal. Evidence of consolidation (dullness on percussion, bronchial breath sounds, and egophony [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.[89] Patients with *Mycoplasma, Pneumocystis,* tuberculosis, or viral infection may exhibit few abnormalities at physical examination despite the presence of impressive infiltrates on chest images.

The overall usefulness of the history and physical examination to detect the presence of pneumonia has been questioned.[90] 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%.[90]

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 usefulness. Several studies have assessed the use of clinical prediction rules for determining the presence or absence of pneumonia based on multiple physical findings.[91] The absence of any vital sign abnormalities (i.e., respiratory rate >20 breaths/min, heart rate >100 beats/min, and temperature >37.8°C) 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 that pneumonia is present to 40% to 50%. Therefore, although variable and nondefinitive, a complete history and physical examination may be extremely helpful in guiding the workup of pneumonia (see Table 67.3).

Diagnostic Testing

Clinical features derived from a careful history and physical examination and confirmed with radiographs of the chest that show 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 of CAP, especially mild-to-moderate cases. Studies comparing empirical therapy and laboratory-guided pathogen-directed care have shown no differences in efficacy, although increased side effects were noted in the patients receiving empirical therapy.[92] 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 and to use 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 reveal 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 define the cause of CAP in up to 89% of cases as compared with only 39% with culture.[93] However, molecular techniques to identify bacteria are not widely available, add to the cost of care, and include falsely positive findings that represent colonization rather than disease.[94] Guidelines from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (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."[95]

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 who do, approximately 40% to 60% of samples may be judged to be inadequate for further study because of oropharyngeal contamination.[96,97] Many patients have received antibiotics before the studies are carried out, which drastically reduces the diagnostic yield. A variety of organisms cannot be detected with 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.[98] Despite its pitfalls, the sputum Gram stain is noninvasive, can be carried out at no risk to the patient, and under the right circumstances may aid in the diagnosis and choice of empirical therapy in patients with CAP.[99,100] For example, the absence of MRSA in sputum culture or nasal swab may allow the clinician to stop empirical therapy for this pathogen.[101]

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.[102] 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.[103] Dark red, mucoid sputum (currant-jelly sputum) suggests Friedlander pneumonia caused by encapsulated *Klebsiella pneumoniae* (Fig. 67.1).[104] Foul-smelling sputum is associated with mixed anaerobic infections most commonly seen with aspiration or lung abscess.[88]

To maximize the diagnostic yield of the sputum examination, most microbiology laboratories use a scoring system to process only samples with minimal oropharyngeal contamination and reject those with likely oral pharyngeal contamination. There are no definitive guidelines, but 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.[105] Samples with more epithelial cells and fewer neutrophils are usually nondiagnostic and should be discarded. These criteria are problematic in neutropenic patients, and require notification of the laboratory if the provider believes that the culture should be processed. Morphologic and staining characteristics of any bacteria seen should be recorded and an estimate made of the predominant organisms (Figs. 67.2 through 67.6). When no bacterial predominance exists, this should also be noted.

In the appropriate clinical setting, a predominance of gram-positive, lancet-shaped diplococci should suggest pneumococcal infection (see Fig. 67.2). 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%.[106] 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.[107] However, it is our experience that the large number of pneumococci necessary to produce a positive Gram stain is unusual in carriers.

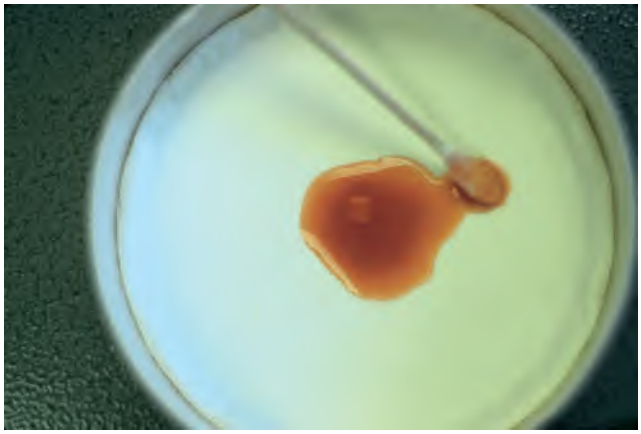

FIG. 67.1 **"Currant-jelly" sputum associated with *Klebsiella pneumoniae* pneumonia.**

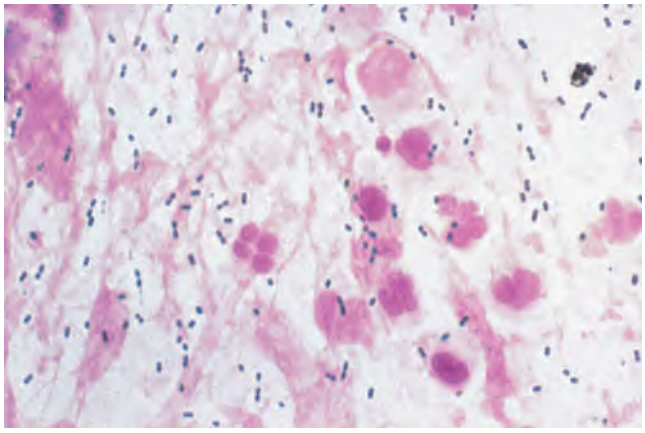

FIG. 67.2 **Expectorated sputum with gram-positive, lancet-shaped diplococci from a patient with pneumococcal pneumonia.**

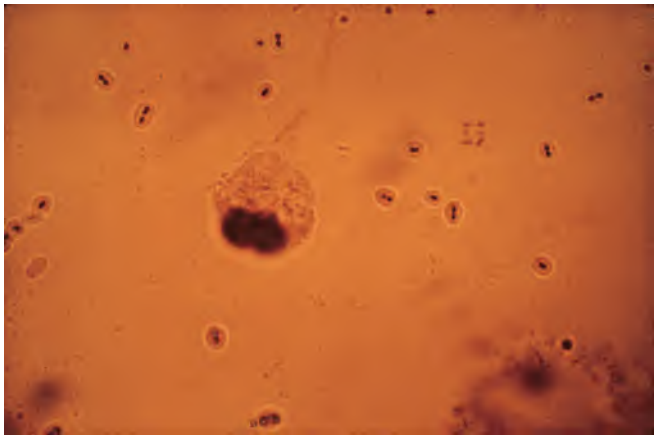

FIG. 67.3 **Expectorated sputum demonstrating a positive quellung reaction in a patient with pneumococcal pneumonia.**

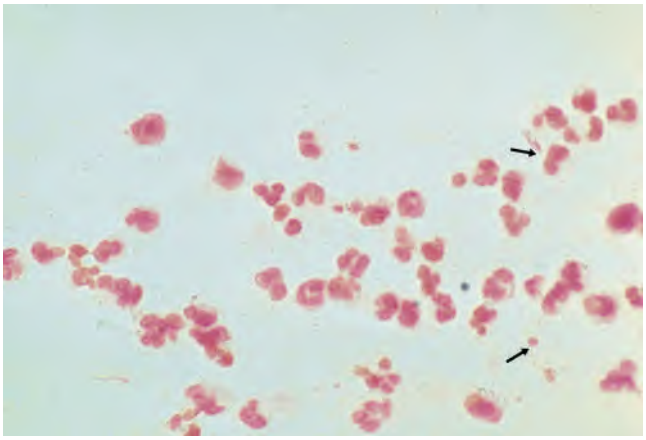

FIG. 67.4 Expectorated sputum with gram-negative coccobacillary forms *(arrows)* from a patient with *Haemophilus influenzae* pneumonia.

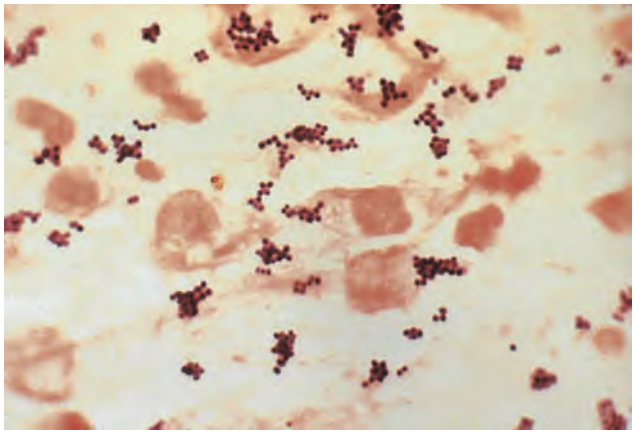

FIG. 67.5 Expectorated sputum with clusters of gram-positive cocci in a patient with *Staphylococcus aureus* pneumonia.

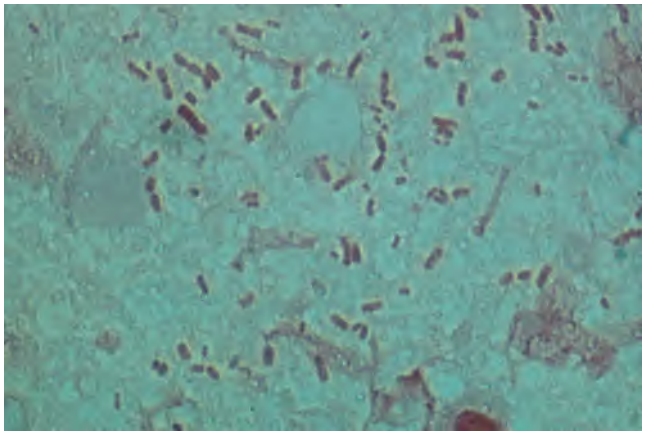

FIG. 67.6 Expectorated sputum with gram-negative rods in a patient with *Klebsiella pneumoniae* pneumonia.

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. 67.4). 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. 67.5). 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

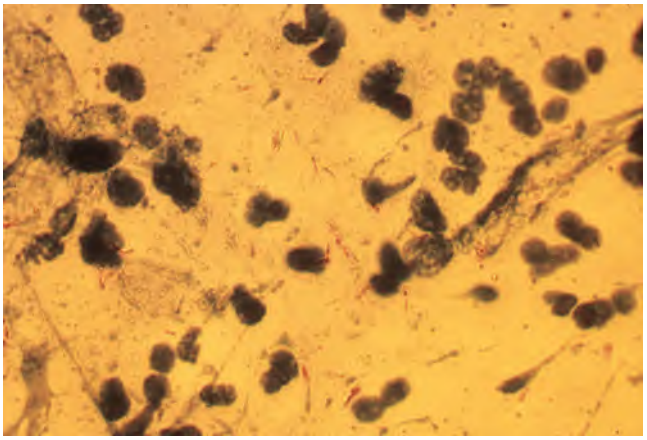

FIG. 67.7 Expectorated sputum with acid-fast bacilli in a patient with *Mycobacterium tuberculosis* infection.

patients undergo nebulizer treatment with 3% saline solution and PCR techniques on oropharyngeal wash has been a useful means of diagnosing *Pneumocystis* pneumonia in patients with AIDS[108] and may be useful in other immunocompromised patients who have trouble producing sputum. Special sputum staining techniques are important in identifying other organisms such as mycobacteria (Fig. 67.7) or *Nocardia* species.

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%.[98] Similarly, only 35% to 73% of sputum cultures are positive with proven *H. influenzae* pneumonia.[109,110] 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.[111]

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 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.[98]

Antigen detection in respiratory secretions has been used for over several 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 *P. jirovecii* are the most commonly used, with sensitivities of 25% to 75% for *Legionella* and 80% for *Pneumocystis.*[112,113] The sensitivity for *Pneumocystis* may be less for patients with causes of immunosuppression other than HIV disease.[114] 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 secretions and sputum, remains an area of ongoing study.[115–118] Nucleic acid amplification assays, especially polymerase chain reaction (PCR) assays, 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. Although a variety of PCR techniques have been described, US 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,* and *Mycoplasma* and *Chlamydia* spp. have been developed, and study protocols have advanced our understanding of the etiology of pneumonia, but lack of standardization and also cost have limited usefulness clinically. The FDA has approved multiplex PCR techniques that test for over 20 viral and bacterial pathogens with use of nasopharyngeal swabs and that can be performed at the point of care. Further studies have been proposed in order to investigate the usefulness of such testing in clinical practice.[118] PCR assays can also detect *P. jirovecii,* although the usefulness of PCR remains under debate because it appears sufficiently (overly) sensitive to detect asymptomatic colonization in addition to clinical disease, and a quantitative PCR technique will be necessary for clinical usefulness.[119] 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 50% to 70% in patients who are AFB smear negative even in low-incidence settings; specificities as high as 99% have been noted.[120,121] However, PCR assay results 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.[116] The test systems differ for viral pathogens that they detect. Available assays can detect influenza A, influenza B, parainfluenza viruses, respiratory syncytial viruses (RSVs), human metapneumovirus, coronaviruses, adenovirus, rhinovirus or enterovirus, 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. These molecular assays have clear utility for research purposes.[67,93] 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 bronchoalveolar lavage (BAL) or transbronchial biopsy or both.[122] BAL, in which a segment of the lung is washed with sterile fluid, samples approximately 100 million alveoli and consequently enables examination of 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.[123]

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.[124–126] 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.[127] The use of antibiotics markedly diminishes the diagnostic yield of the procedure. Most bacterial species initially found with 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.[124] BAL has also been used for the diagnosis of atypical pneumonias, including those caused by *Legionella* species and *M. pneumoniae.* In research settings, BAL with multiplex PCR may be helpful and lead to targeted treatment and improved antibiotic stewardship.[128] Only the specific nasal pharyngeal tests for *Chlamydia* and *Mycoplasma* are FDA approved, but the broadly diagnostic BioFire panel has also been approved.

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.[129] Excellent yields have also been noted in detecting cytomegalovirus (CMV) in patients with AIDS and in bone marrow and solid organ transplant recipients, although detection of this agent alone does not prove it the cause of pneumonia because it frequently blooms in immunocompromised hosts; most patient with CMV pneumonitis have evidence of CMV by PCR in blood.

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.[130] With use of strict diagnostic definitions, PCR and galactomannan assays on BAL have approximate sensitivities and specificities of 77% and 93% for invasive pulmonary aspergillosis.[131] Bronchoscopy with calcofluor staining and fungal culture can also be helpful in the diagnosis of pulmonary histoplasmosis, cryptococcosis, and coccidioidomycosis.[122,132,133]

Both bronchoscopy and BAL have been used widely in patients with ventilator-associated pneumonia (VAP).[134] The IDSA/ATS guideline on VAP recommends noninvasive sampling or endobronchial aspiration to help determine the specific bacteriologic cause. However, 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 in patients with suspected VAP.[135]

Bronchoscopy is not without risk. It can induce respiratory failure and the need for mechanical ventilation in hypoxemic patients. There is a risk of bleeding with both the use of protected brush catheters and transbronchial biopsies, in addition to the lesser risk of 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 if there is a clear failure of antibiotic therapy. This might suggest an occult process such as an obstructing malignancy, a minor obstructing lesion, or a foreign body not seen at diagnostic imaging.[122]

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.[136] With a threshold of greater than 10^5 colony-forming units (CFUs) per milliliter, the sensitivity for predicting VAP was comparable to that of lavage or protected brush procedures, although the specificity was somewhat lower.[136] Furthermore, no differences in mortality, length of stay in the ICU, or duration of mechanical ventilation were noted when quantitative endotracheal cultures were used as the sole means of diagnosis compared with BAL and with protected specimen brush. Others have reported false-negative rates of over 30% and many more organisms isolated with endotracheal suctioning than with

brushing.[137] In addition, in the setting of VAP, concern remains about sampling error and 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.[138,139]

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. Computed tomography (CT)–guided percutaneous lung aspiration has been shown to be effective in diagnosing focal fungal infections in the transplant population.[140] Open lung or video-assisted lung biopsy remains the definitive invasive procedure for making an etiologic diagnosis of pneumonia in immunosuppressed patients, with diagnostic yields of 60% to 100%.[141,142] In immunocompromised patients, the incidence of unexpected diagnoses that can lead to a change in treatment can be over 50%.[143] The incidence of pneumothorax and bleeding is usually less than 10%,[141] although the overall complication rate is 22% to 28% in patients with acute respiratory distress syndrome (ARDS) or after solid organ transplantation.[143]

Examination of Pleural Effusions

The characteristics of pleural effusions and their importance in the differential diagnosis of pulmonary disease are discussed in Chapter 68. 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.[144–146] The incidence of pleural effusions associated with pneumonia varies with the etiologic agent, from approximately 40% to 57% with pneumococci, to 50% to 70% with gram-negative bacilli, and up to 95% with β-hemolytic streptococci.[103,147] 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 and in differentiating other causes of pulmonary infiltrates that may mimic bacterial pneumonia, including tuberculosis, tumors, pulmonary emboli, and collagen vascular diseases. Thus, pleural fluid analysis should be strongly considered in patients with apparent pneumonia and pleural effusion when the radiologic findings are not consistent with fluid overload. 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.[144,147] The first stage, or exudative stage, is culture negative, has a pH of greater than 7.2, glucose greater than 60 mg/dL, and a lactate dehydrogenase (LDH) 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 that 7.2, glucose less than 60 mg/dL, and LDH that is greater than three times the upper limit of normal. Such complicated pleural effusions require drainage. The most sensitive finding in determining whether 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.[144] 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 wherein a thick pleural rind is formed, restricting 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.[148,149] Other diagnostic tools have proven useful in identifying organisms associated with pleural effusions. PCR technology can be useful in detecting *M. tuberculosis* and in defining the cause in culture-negative cases.[149,150] Adenosine deaminase, an enzyme associated with lymphocytes, may also be used to detect *M. tuberculosis,* with reported sensitivity and specificity of over 90%,[151,152] but actual performance in the field appears to be lower.

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

Blood cultures are positive in 4% to 17% of patients hospitalized with CAP, with the frequency of positive results increasing with the severity of illness.[93,123,153–155] Some studies have suggested that positive blood cultures add little to the management of patients hospitalized with CAP and are not predictive of increased mortality.[156–158] 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 with routine empirical antibiotic coverage.[159,160] Work has shown that several clinical features can be used to predict patients with a higher likelihood of having bacteremia.[154,155] 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.[155] It is clear that blood cultures should be obtained before antibiotic administration in all patients with CAP who are ill enough to be hospitalized who have two or more of these features, and in those patients who are immunocompromised, who have been admitted with health care–associated pneumonia (HCAP), or who acquire pneumonia in the hospital. The IDSA and ATS have also recommended blood cultures for patients who are admitted to an ICU and have a cavitary lesion, leukopenia, active alcohol abuse, asplenia, a positive pneumococcal urinary antigen, or a pleural effusion.[95] Furthermore, because the cause of pneumonia is not always found, assessment of clinical response to initial therapy is important, and blood cultures should be obtained in patients not responding to antibiotic therapy.[160]

A variety of assays have been used to detect pathogens that have been difficult to isolate with routine culture techniques. Serologic assays have been used to diagnose infections caused by *Legionella* species, *M. pneumoniae, Chlamydia* species, and *Coxiella burnetii.* The sensitivity and specificity of the assays vary, and their overall usefulness for 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.[161] Microimmunofluorescence (MIF) for serum chlamydial antigens has been recommended, although enzyme immunoassays (EIAs) are also available and may be more sensitive and specific.[162] 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.*[163] Although an elevated IgM titer suggests a recent infection, reinfection with *Mycoplasma* occurs frequently, and a rise in IgM may not always be seen.[164] 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, and in general have resulted in notably lower rates of positivity than serologic

studies, suggesting that the latter likely have much lower specificity for acute infection than was previously recognized.[163,165,166]

S. pneumoniae produces a variety of antigens and surface markers that are type or species specific.[167] Although both antigen and antibody detection methods in serum have been studied, none have become clinically significant. PCR techniques have been applied to whole blood for the detection of pneumococci, but the assays remain experimental.[168]

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 in addition to immunocompetent individuals suspected of having infection with *Cryptococcus gattii.*[169] 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, and for the detection of pneumonia due to the endemic fungi *Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis* in patients who have appropriate geographic exposure.[170–172] 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.[171,173]

A variety of cytokines are released into the circulation as a result of infection.[174–177] Evidence suggests that these biomarkers may be useful adjuncts in diagnosing pneumonia and predicting severity of disease.[174–177] The calcitonin family of gene products, especially procalcitonin, C-reactive protein (CRP), 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 (>0.25–0.5 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 of an adverse outcome.[178–180] Still, the usefulness of this marker in antibiotic stewardship programs remain unresolved.[181,182] Procalcitonin has also been used as a gauge of pneumonia-related mortality.[183] CRP 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).[177] In comparative trials with procalcitonin, CRP appears to have a better ability to define infection and procalcitonin the clinical severity, although definitive studies are lacking.[176] 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.[184,185] 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.[182,186]

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 EIA. 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% for this serogroup.[112] 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).[187] This has been reported to be an extremely useful means of diagnosing pneumococcal pneumonia. With use of a variety of standard diagnostic tests as controls, overall sensitivities of 65.5% to 100%, specificities of approximately 94% to 100%, and positive predictive values of 62% have been noted.[188–190] 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 non-pneumococcal organisms, false-positive results in children with nasopharyngeal carriage rather than true infection, and positive results lasting for weeks after the infection has resolved.[161,189] Shortfalls of the test are that no organism is isolated, and thus 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, although in hospitalized patients it may allow deescalation of antibiotics.[191]

Radiologic Examination

Chest radiography plays a critical role in the diagnosis of pneumonia, and it represents the gold standard of making a clinical diagnosis. 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 of upper respiratory infections has been documented and may contribute to the growing problem of antibiotic resistance, identifying patients who really should be receiving antibiotic therapy is important. The chest radiograph is readily available, is reasonably reliable (despite interobserver variability), and should be obtained in many patients suspected of having pneumonia.[95,192,193] The extent and nature of radiographic abnormalities may define patients who are more seriously ill and may need close monitoring.

The infiltrate patterns found on chest radiographs in patients with pneumonia usually are not helpful in making a specific etiologic diagnosis (Fig. 67.8A–B).[193] However, certain features may be of some diagnostic aid (Table 67.4). Lobar consolidation, cavitation, and large pleural effusions support a bacterial cause (Figs. 67.9 and 67.10). 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. 67.11). *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.[194,195] 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.[196] The radiographic concomitants of these pathologic findings usually involve patchy areas of peribronchial ground-glass opacity, air-space consolidation, and poorly defined small nodules. Diffuse and localized involvement with both interstitial and alveolar patterns has been noted (Fig. 67.12).[196] There is little radiologic distinction among the various viral causes of pneumonia. Influenza pneumonia is associated with poorly defined, patchy air-space consolidation with rapid confluence. Varicella pneumonia usually involves peribronchial involvement with nodular infiltrates. Adenovirus, herpes simplex, and CMV, all of which are more common in immunocompromised hosts, may be associated with diffuse bilateral

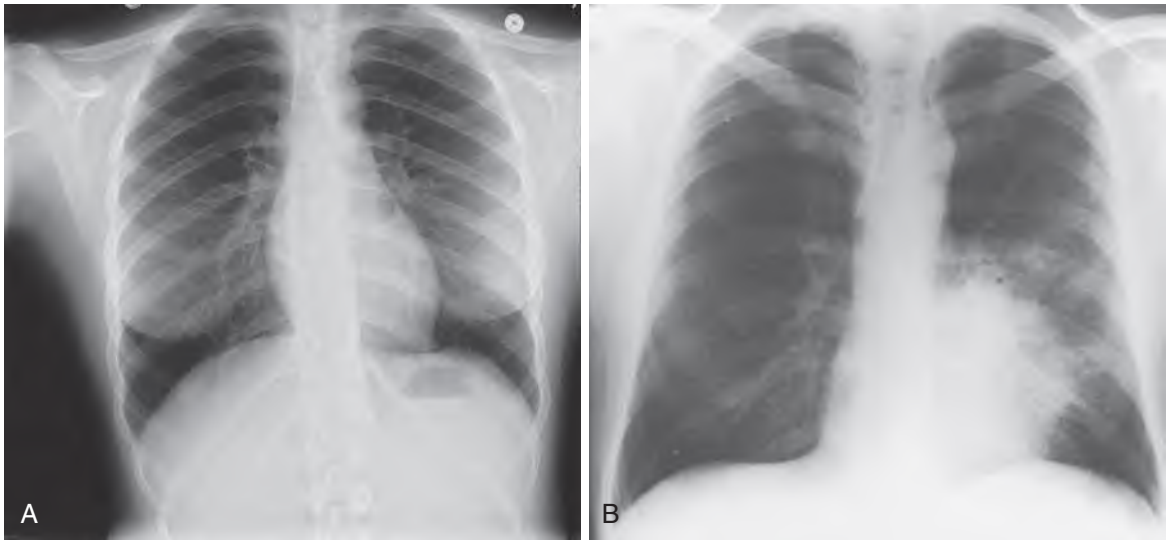

FIG. 67.8 (A) Normal chest radiograph. (B) Patchy infiltrate representing bronchopneumonia in a patient with *Streptococcus pneumoniae* infection.

bronchopneumonia, areas of overinflation, atelectasis, and nodular opacities. Lobar or subsegmental consolidation mimicking bacterial pneumonia may also be seen with adenovirus and herpes simplex. Hantavirus pneumonia usually manifests with interstitial edema, which may progress to consolidation representing a pulmonary capillary leak syndrome. Bilateral involvement and pleural effusion are common and when present are associated with a worse clinical outcome.[197] 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 air-space disease.[198–200] Other recently defined viral pulmonary pathogens are the human metapneumovirus and bocavirus. Most cases of human metapneumovirus involve upper respiratory tract infections in children; pneumonia in adults has been described.[201,202] 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, similar to the other common respiratory viruses.[203]

Mycoplasmal pneumonia often manifests with an interstitial pattern in a peribronchial and perivascular distribution.[204] 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.[204,205] *Chlamydia pneumonia*e predominantly causes unilobar disease with associated air bronchograms.[193]

Legionnaires' disease may initially manifest with a radiographic picture similar to that of mycoplasmal pneumonia. A patchy interstitial or finely nodular pattern is seen in the lower lobe.[206] 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 manifest with pulmonary nodules, either single or multiple, and with segmental infiltrates. As in pneumonia caused by *L. pneumophila,* rapid radiologic progression of the disease is characteristic.[207]

Chest CT scanning has been shown to improve radiographic characterization of lung infection.[208–210] In the immunocompetent host, chest CT may reveal infiltrates not present on chest radiograph at the time of initial presentation to an emergency room and may rule out CAP in some patients.[211] Chest CT is helpful in evaluating recurrent pneumonia, a chest radiographic abnormality such as a carcinoma that predisposes to pneumonia, or infections unresponsive to therapy. Pneumonia developing behind an obstruction caused by a tumor, other masses, or a foreign body, and lung abscess are better defined on CT scans than on routine chest radiographs.[208] However, exposure to more radiation (the radiation from one CT scan equals that from six to seven chest radiographs) and the increased expense 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.[209] In the immunocompromised host in whom infection is only one of the possible causes of abnormal chest radiographs, chest 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 and in patients older than 65 years. 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 films.[210] Techniques such as perfusion magnetic resonance imaging and nuclear medicine procedures are generally not used in patients with CAP. Early in the AIDS epidemic, gallium scans were used to help diagnose *Pneumocystis* infection even in patients with normal chest radiographs.

PNEUMONIA SYNDROMES

Acute Community-Acquired Pneumonia

An extensive 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.[212,213] Increases in numbers of patients living longer, more and varied comorbidities, the increasing use of biologic immunomodulators such as TNF inhibitors, expanded contact with various aspects of the health care system, and decreases in the prevalence of *S. pneumoniae* and *H. influenzae* type B due to vaccine usage 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 mid fifties to late sixties. Peak incidence of bacteremic pneumococcal disease in general occurs in midwinter and early spring, and disease due to *Legionella* is more frequent in the summer.[211,214] Still, there is no "pneumonia season," and disease occurs throughout the year. Most patients (58%–89%) have one or more chronic underlying diseases. Immunosuppression related to HIV infection, malignancy, neutropenia, the chronic use of steroids, myelosuppressive agents, and newer immunosuppressive agents for

TABLE 67.4 Guide to Differential Diagnosis of Pneumonia Based on Radiologic Characteristics

IMAGING CHARACTERISTICS	POSSIBLE PATHOGENS
Chest Radiograph	
Dense segmental or lobar consolidation	More likely bacterial pathogens
Unilateral or bilateral homogenous consolidation	*Streptococcus pneumoniae, Legionella* spp., *Mycoplasma pneumoniae*
Lower lobe	Aspiration-anaerobes, gram-negative rods
Unilobar with air bronchograms	*Chlamydia*
Bulging fissure sign	*Klebsiella* spp.
Bronchopneumonia—result of bronchial inflammation, epithelial ulceration, fibropurulent exudate	*Staphylococcus aureus, Haemophilus influenzae*, fungi
Interstitial infiltrates or interstitial-alveolar infiltrates (diffuse pneumonitis)	More likely viral or *Mycoplasma*
Bilateral with hypoxia out of proportion to imaging abnormalities	*Pneumocystis jirovecii* (PCP)
Patchy, peribronchiolar opacities or ill-defined reticulonodular opacities	Primary viral infection including CMV, HSV, adenovirus *M. pneumoniae*
Diffuse bilateral bronchopneumonia	CMV, HSV, adenovirus,
Unilateral or bilateral interstitial basilar infiltrates progressing to severe symmetrical air-space disease	Coronavirus including SARS, MERS
Cavitary Lung Lesions	
Upper lobe	Tuberculosis or nontubercular mycobacteria
Unilateral or lower lobe	Anaerobic lung abscess
Multiple, may be pleural based	Endemic and opportunistic fungi
Cavities that evolve from lobar consolidation and coalescence of latencies	*S. aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae*
Pleural effusion	Large effusions support a bacterial cause
In association with necrosis, pneumatoceles or empyema	*S. aureus*, *Streptococcus pyogenes, S. pneumoniae*
With multilobular infiltrates	Primary viral especially metapneumovirus, bocavirus
Pneumatoceles	*S. aureus*, *Klebsiella* spp., *Haemophilus* spp., *S. pneumoniae*
Multiple nodules	Bacteremic spread of *S. aureus* Endemic or opportunistic fungi
Parabronchial	Varicella zoster virus
Hilar adenopathy	
With upper lobe infiltrate	*Mycobacterium tuberculosis*
With homogenous opacities, may cavitate	Coccidioidomycosis
With signs of obstruction	Malignancy with bacterial infection
Computed Tomography	
Ground-glass opacities—localized increase in lung attenuation	*Pneumocystis, Mycoplasma,* fungi, CMV and other viruses
Tree-in-bud pattern—reflects presence of bronchioles filled with inflammatory material	Bacteria, mycobacteria, fungi, viruses including RSV and parainfluenza virus, and other atypical pathogens

CMV, Cytomegalovirus; *HSV,* herpes simplex virus; *MERS,* Middle East respiratory syndrome; *PCP, P. jirovecii* pneumonia; *RSV,* respiratory syncytial virus; *SARS,* severe acute respiratory syndrome.

Data from Franquet T. Imaging of pneumonia: trends and algorithms. Eur Resp J. *2001;18:196–208, and Franquet T. Imaging of community-acquired pneumonia.* J Thorac Imaging. *2018;33:282–294.*

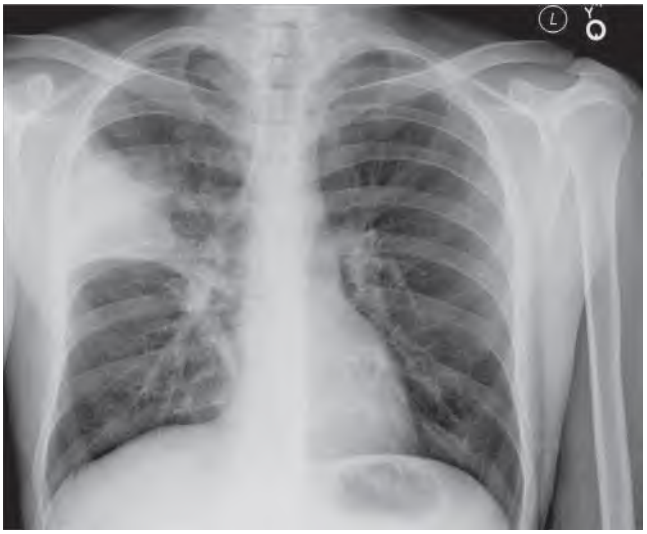

FIG. 67.9 Focal airspace consolidation within the right upper lobe posterior segment, compatible with bacterial pneumonia in a patient with *Streptococcus pneumoniae* infection.

FIG. 67.10 Pneumatocele formation in the left upper lobe of a patient with staphylococcal pneumonia.

treatment of rheumatologic, dermatologic, and gastrointestinal disease is being increasingly observed.

On a historic basis, CAP manifested with a sudden onset of a chill followed by fever, pleuritic chest pain, and cough that produced mucopurulent and rusty sputum. While this classic presentation is still seen occasionally, 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.[215] Cough is noted in more than 80% to 90% of patients and is productive in over 60%.[59,215–217] Chest pain is present in approximately 35% to 48% of patients, chills in 40% to 70%, and hemoptysis in approximately 15%.[59,215,216]

A variety of nonrespiratory symptoms are associated with pneumonia, including fatigue (91%), anorexia (71%), sweats (69%), and nausea (41%).[59] Both respiratory and nonrespiratory findings occur less frequently in older age groups.[60]

Physical examination reveals fever in 68% to 78% of patients, but it may be seen less commonly in older populations. Tachypnea (respiratory rate greater than 24–30 breaths/min) is noted in 45% to 69% of patients and may be more frequently seen in older age groups.[60] Tachycardia (pulse rate greater than 100 beats/min) is noted in approximately 45% of patients, rales in approximately 70% of patients, and

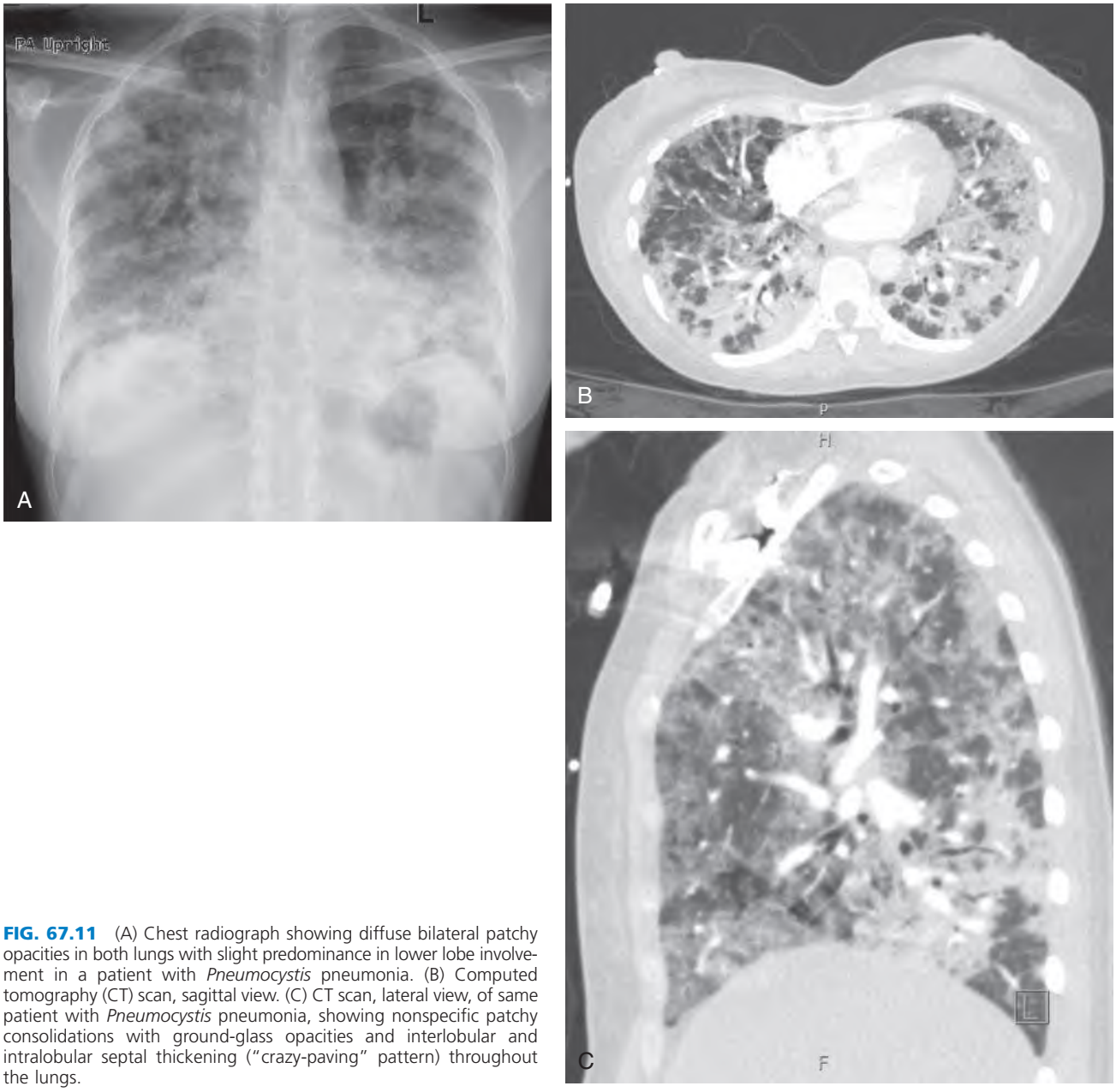

FIG. 67.11 (A) Chest radiograph showing diffuse bilateral patchy opacities in both lungs with slight predominance in lower lobe involvement in a patient with *Pneumocystis* pneumonia. (B) Computed tomography (CT) scan, sagittal view. (C) CT scan, lateral view, of same patient with *Pneumocystis* pneumonia, showing nonspecific patchy consolidations with ground-glass opacities and interlobular and intralobular septal thickening ("crazy-paving" pattern) throughout the lungs.

signs of consolidation in 20%.[215] However, no combination of physical findings has been found to be adequate to confirm a diagnosis of pneumonia.[59]

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.[95] The hematocrit and the red blood cell indices are usually normal.

With classic CAP, the 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.

In the early 1900s, microbiologic studies defined *S. pneumoniae, H. influenzae, S. aureus,* and enteric gram-negative bacilli as the predominant causes of the typical CAP syndrome. Then 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.[218] 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 (characteristics of illness with these pathogens are detailed later). 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. Historically, the epidemiology and clinical features of the atypical pneumonias were thought 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; and in addition, in approximately one-third of cases more than one pathogen can be identified, most commonly a combination of viral and bacterial agents.[84,219]

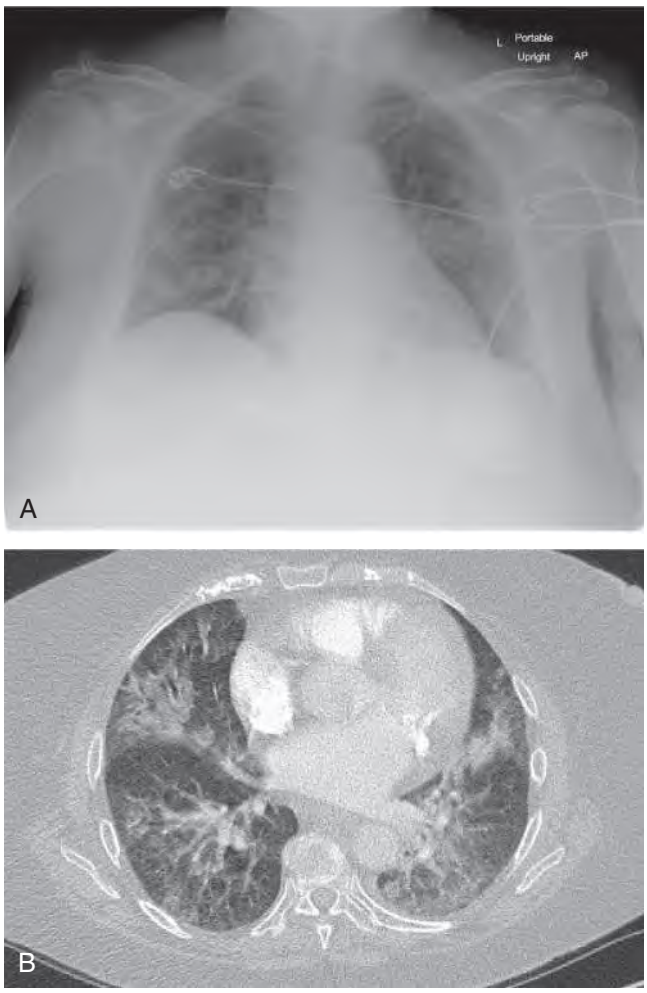

FIG. 67.12 (A) Chest radiograph showing patchy opacities in the right lower and left mid and lower lung zones in a patient with human metapneumovirus pneumonia. (B) Computed tomographic scan, sagittal view, showing extensive patchy ground-glass consolidations in all lobes of the lungs of same patient with human metapneumovirus, obtained 3 days after chest radiograph.

In the past, 40% to 80% of cases of acute CAP appear to have been caused by *S. pneumoniae.*[99,220] More recent studies have found that the relative frequency has diminished in the developed world, although not in developing countries.[84,219,221–223] It has been defined as the cause of pneumonia in as few as 4% to 6% of ambulatory patients and hospitalized patients.[84,224,225] It has been hypothesized that the apparent decreased incidence of pneumococcal pneumonia has been related to the recognition of newer pathogens and diminished use and performance of microbiologic studies.[99] However, through a herd immunity effect, the increasing use of pneumococcal vaccine in children has reduced the incidence of pneumococcal disease in both children and adults in the developed world.[226,227] Severe pneumococcal infections, including pneumonia, have been associated with prior splenectomy due either to trauma or to staging for Hodgkin disease; abnormal immunoglobulin responses (myeloma, lymphoma, HIV infection); and functional asplenia due to systemic lupus erythematosus or marrow transplant.[228,229]

Improved diagnostic testing with more sensitive nucleic acid amplification tests has shown that community respiratory viruses play a significant role in pneumonia both as single agents and in dual infections.[84,219,222,230] Studies have suggested a viral cause in up to one-third of adults and children hospitalized with pneumonia. Influenza A and B, RSV, human metapneumovirus, parainfluenza virus, and coronavirus are the most frequently identified viral pathogens. In addition, up to half of the patients with a viral pathogen identified will have concurrent bacterial infection, and multiple concurrent viral pathogens can also be seen.[84,219,222] Whether rhinoviruses are a direct cause of pneumonia remains unresolved, but they have been found in patients with severe pneumococcal disease, and in vitro have shown increased adherence of *S. pneumoniae* to human tracheal epithelial cells.[231,232] Consequently it is possible that these viruses play a role as facilitators for bacterial infection rather than roles as true pulmonary pathogens.

S. aureus accounts for 1% to 2% of acute CAP cases,[84,224,225] and may take on increased importance as a cause of pneumonia in older adults and in those with influenza.[63,233] Patients who develop postinfluenza pneumonia are usually younger and have less underlying disease than most other patients with CAP. Although it had been felt that bacterial pneumonia in the setting of influenza develops following clinical influenza, studies during the 2009 H1N1 pandemic indicated that bacterial coinfection most likely arises at the peak of viral replication, with patients presenting an average of 6 days after symptom onset.[63] 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 lung infection secondary to a bacteremic source, 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.[234,235]

As noted previously, since the late 1990s there has been an increase in the incidence of pneumonia due to community-associated *S. aureus* strains.[195,236] Patients have been young, have had few if any comorbidities, and usually have presented after a flulike illness with high fevers, leukopenia, tachycardia, tachypnea, hemoptysis, and rapid evolution on radiographs to multilobar disease. These cases appear to be associated with *S. aureus* strains carrying the Panton-Valentine leukocidin toxin, regardless of whether or not they are methicillin resistant.[237] The adult respiratory distress syndrome has been a frequent complication in such cases, and mortality rates of over 50% have been seen.[195]

Aerobic gram-negative bacteria, exclusive of *H. influenzae,* may cause anywhere from 2% to 10% of pneumonia cases. *K. pneumoniae, P. aeruginosa,* and *Enterobacter* spp. are the organisms isolated most often.[84,224,225,238] 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 species are the most important water-related pulmonary pathogens in the United States with regard to mortality and morbidity. The importance of *Legionella* species in causing pneumonia has varied greatly in different geographic areas, with incidences ranging from 0.6% to 23%.[212,213,215,221,239] Since 2000 there has been a fourfold increase in incidence of legionellosis in the United States, although it is not clear how much of this increase has been related to increased diagnostic testing.[240] 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), 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.[213,239] However, no clinical features reliably distinguish *Legionella* species pneumonia from that caused by other bacteria.

Historically an estimated 5% to 7% of cases of acute CAP were attributed to *H. influenzae.*[221,224,225] The true incidence of this organism was obscured by the difficulty of isolating it from sputum and identifying it in sputum Gram stain, and by the difficulty of distinguishing colonization from infection. However, the use of the *H. influenzae* conjugate vaccine, by decreasing the reservoir in children, has markedly decreased the incidence of invasive disease caused by *H. influenzae* type b, and

although there has been a relative increase in the incidence of invasive infections caused by nontypeable strains, population-based studies have indicated that the pathogen causes only 1% to 5% of pneumonia necessitating hospitalization in adults and children.[84,219,222]

M. catarrhalis has also been identified as a cause of pneumonia.[219,221,224,225,241] 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.

A number of additional pathogens including *M. pneumoniae, Chlamydia* species, *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 *S. pneumoniae.*[221]

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.[242] 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 310). For those over the age of 60, pneumonia is a predictor of increased mortality after the specific episode has resolved and for several years thereafter.[243]

The clinical presentation of pneumonia in older adults (especially those over 80 years of age) may be subtler than in younger populations, with more gradual onset of symptoms and fever and the classic signs of pneumonia.[60,83,213] 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.[82,244] Chills and rigors may also be less frequently seen. Tachypnea (respiratory rate of greater than 24–30 per minute) and rales are more frequent findings in older adults and have been observed in up to 65% of patients.[60,83] 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.[244] The development of in-hospital complications and death are more frequent in older populations.[83]

Specific etiologic diagnoses are made less frequently in older adults, with approximately 20% to 50% of patients having an etiologic agent defined.[83] The absence of productive cough and common prior use of antibiotics may explain this observation. Etiologies have varied in different series depending on the means of diagnosis, the patient population studied (outpatient vs. institutionalized older adults), and the geographic location.[84] In general, the cause of CAP in the older population follows the general trend of infection in younger populations. Community respiratory viruses and *S. pneumoniae* remain the predominant pathogens, and there is an increased frequency of aspiration pneumonia.[83,242] Major viral pathogens in the elderly include influenza A and B, parainfluenza virus, human metapneumovirus, RSV, and coronaviruses. In addition, rhinovirus is also frequently identified, as both a single pathogen and a copathogen, and appears to potentiate bacterial copathogens if not pathogenic in the lower respiratory tract.[231,232] *H. influenzae,* usually a nontypeable strain, was the second most common agent in the past, accounting for 5% to 10% of episodes,[83,245] but appears to be a less frequent pathogen today.[84] 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 but not all 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 thought 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.[246] 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.[238] In this regard, one study of apparent aspiration pneumonia in a nursing home population older than 65 years of age that used protected BAL to define the microbiologic etiology identified gram-negative bacteria as the primary pathogen in 49%, followed by mixed anaerobes in 16%.[247] 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.[82,83]

It is not completely clear which agents cause atypical pneumonia in the older population. Most series suggest that *M. pneumoniae* pneumonia is unusual, although it has been documented to be a cause of pneumonia leading to hospitalization in older adults.[62,82–84] It is not clear if this significant variation is related to differing epidemiologic characteristics of study populations or to the accuracy of diagnostic methods. *Chlamydia* infections have been reported in the older population, and in one study were associated with 32% of pneumonias on the basis of serologic testing; but again, there is a significant variation in incidence in differing studies and the relative incidence has been lower in more recent studies that have used nucleic acid amplification assays.[62,82–84,219,220,248]

Severe Community-Acquired Pneumonia

Approximately 10% of patients with CAP will develop severe disease as defined by admission to an ICU owing to the presence of shock necessitating vasopressors or respiratory failure necessitating mechanical ventilation.[249] 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 thought to be associated with the development of severe CAP.[249] 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* species), and *H. influenzae.*[221,250,251] As with CAP in general, newer molecular tests indicate that the community respiratory viruses are frequent copathogens with severe pneumonia and can be the sole identified pathogen.[252] *Pneumocystis* is increasingly being recognized as a cause of severe pneumonia in non–HIV-infected patients who have impaired cell-mediated immunity owing to organ transplantation, malignancy, severe malnutrition, or receipt of immunosuppressive therapies including corticosteroids, antineoplastic chemotherapeutic agents, and newer agents including TNF-α inhibitors and rituximab.[253–255] 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 that despite the overall mortality rate for CAP of 13.7%, it was 36.5% for patients with disease severe enough to require ICU care.[256] Unfortunately, more recent studies have continued to find comparably high mortality in this patient population.[257,258] 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 and 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 last 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)[249]; the *c*onfusion, *u*rea, *r*espiratory rate, low *b*lood pressure (CURB) score[259]; the CURB plus age >65 (CURB-65) score[260]; the CURB-65 score without the urea level (CRB-65)[261]; the severe community-acquired pneumonia (SCAP) score[262]; the SMART-COP score[263]; and the Risk of Early Admission to the Intensive Care Unit (REA-ICU) index.[264] These rules vary in complexity

and in their sensitivity and specificity for defining the need for ICU care, but use a combination of factors including age, sex, 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 will be discussed under the "Management and Therapy of Pneumonia" section of this chapter. In rare cases, severe CAP may be the presentation for anthrax, plague, tularemia, or zoonotic viral infections: the epidemiologic setting is important in this regard.

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. In the 21st century, there has been a shift of health care delivery from inpatient to outpatient settings, and 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. The recognition of this situation in the mid-2000s led the ATS and IDSA to propose a new clinical classification of pneumonia termed *health care–associated pneumonia* that was felt to represent a distinct syndrome that is a hybrid of CAP and hospital-associated pneumonia.[85,86,265] The exact definition used in studies supporting the concept 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.[85] Important to note, the etiology has shifted from typical CAP, with an increased incidence of infections due to aerobic gram-negative bacilli including *P. aeruginosa*; *S. aureus* including MRSA; *S. pneumoniae*; and mixed aerobic-anaerobic pathogens associated with aspiration most commonly reported.[86,266] In addition, the overall mortality is higher in patients with HCAP (10.3%–19.8%) than in CAP (4.3%–10%), and generally comparable to that of hospital-acquired pneumonia.[86,265,266] Because of this concern, relatively broad-spectrum antibiotic therapy including coverage for both MRSA and *P. aeruginosa* has become common for patients meeting the HCAP definition. However, more recent work has challenged the association of HCAP with a high incidence of MRSA and *P. aeruginosa,* and the association of increased mortality with more antibiotic-resistant pathogens.[267,268] It remains unclear whether mortality in patients with HCAP is due to increased comorbidities in patients, more virulent organisms causing infection, an increased incidence of inappropriate antibiotic use in the first 48 hours of care, or some combination of these factors.

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.[269,270] 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.[271] Key modifiable risk factors are inadequate oral care and swallowing difficulties.[272] The subtle presentation noted in other older adult populations also occurs in those in a nursing home setting. *S. pneumoniae* had been considered the predominant cause, but newer studies have identified respiratory viruses as frequent pathogens, in addition to *S. aureus* and gram-negative bacilli in those with severe pneumonia.[248,271] Outbreaks of pneumonia have occurred in nursing homes and have involved *Legionella,* influenza, parainfluenza, RSV, and rhinovirus.[273,274]

"Atypical" Pneumonia Pathogens

Between 10% and 30% of cases of CAP have been attributed in the past to *M. pneumoniae,* with the highest percentage noted in patients well enough to be treated as outpatients, and several studies performed in North America and Europe have suggested that cyclic epidemics occur every 3 to 5 years.[163] *M. pneumoniae* CAP 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, although this organism can cause pneumonia necessitating hospitalization in those older than 60.[62,163,275] An increased incidence of disease and true epidemics have 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 *M. pneumoniae* pneumonia 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 manifests with 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 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 patients.[102] An elevated sedimentation rate is noted in about 25% of 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.[204,205] 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 causes severe CAP, necessitating intensive care.[276] A large number of extrapulmonary manifestations may occur with *M. pneumoniae,* including involvement of skin, central nervous system, blood, and kidneys (see Chapter 183).

C. pneumoniae has been considered an important cause of atypical pneumonia and on the basis of serologic studies was estimated to account for between 6% and 20% of all CAP cases.[62,93,212,215,277–280] Although disease is uncommon in those younger than 5 years, serologic evidence of infection has been noted in over 50% of adults.[62,83,248,281] Disease usually occurs sporadically, but 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 mycoplasma 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 definitive relationship remains unclear (see Chapter 182).

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.[201,202,230,282,283] 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 human bocavirus and human metapneumovirus in children younger than 5 years.[84,222,284–287] 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.[288] 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 (which can cause severe pneumonia), was identified in 2012 (see Chapter 155).[200] 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.[221] *Legionella* species are among the top three our four organisms causing pneumonia that necessitate ICU care.[221,250,251] An international study found that *L. pneumophila* causes over 90% of cases of *Legionella* pneumonia, with approximately 84% of all cases caused by *L. pneumophila* serogroup 1.[289] 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.[290]

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, is noteworthy.[290]

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 LDH 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 postcardiotomy-like syndrome.[290] 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 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 facility cases.[291] 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, and impaired level of consciousness was the major risk factor in an additional 22% of patients.

The pathogenesis of lung injury due to acid aspiration has been delineated.[292,293] 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.[294]

Although aspiration may be a witnessed event, the majority of episodes are silent and are brought to medical attention because of their sequelae.[293] 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 ARDS, 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.[295] Anemia and an elevated white blood cell count are frequently 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 in 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.[296] *Bacteroides* species, *Porphyromonas* species, *Prevotella melaninogenica, Fusobacterium* species, and anaerobic gram-positive cocci are the predominant anaerobes isolated. In community-acquired aspiration pneumonia, *Streptococcus* species 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, and in nursing home patients.[85,247]

Eosinophilic Pneumonias

Pulmonary infiltrates with eosinophilia (PIE), also termed eosinophilic pneumonia, is a syndrome associated with a variety of clinical entities, only some of which have an infectious cause.[297] Pulmonary eosinophilia with transient, peripheral pulmonary infiltrates and minimal symptoms (Löffler 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 disease, paraneoplastic syndromes, and hypersensitivity pneumonitis (e.g., pigeon breeder's disease). A PIE syndrome has been associated with *Pneumocystis* pneumonia.[298]

Acute eosinophilic pneumonia is a distinct clinical entity occurring in younger (20- to 45-year-old), otherwise healthy individuals.[299] It is marked by the acute onset of dyspnea, nonproductive cough, fever, severe hypoxia, and chest pain, and patients may require ICU care and mechanical ventilation. Although leukocytosis is common, peripheral eosinophilia is typically minimal. Bilateral, diffuse pulmonary infiltrates are commonly seen. Radiographic abnormalities usually begin as interstitial infiltrates that progress to alveolar infiltrates. Chest CT reveals bilateral opacities. BAL yields marked (27%–81%) eosinophilia, which is the diagnostic feature of the disease. Although most patients have received antibiotics, rapid stabilization occurs with steroid 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.[300] 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 and migratory infiltrates are commonly seen on radiographs. Interstitial infiltrates and alveolar exudates with a predominance of eosinophils are characteristic pathologic features. A rapid response to steroids 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 thought 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 287).

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.[297,301] 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 with organizing pneumonia (BOOP), Sjögren syndrome, and postradiation pneumonitis are unusual causes of PIE.

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia has been the second most common type of nosocomial infection and is associated with significant morbidity and mortality.[181,302,303] 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* species. The morbidity associated with nosocomial pneumonia includes longer duration of mechanical ventilation and ICU and hospital stays, in addition to an attributable cost of about $40,000.

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 greater than 70 years, severe underlying disease, malnutrition, coma, metabolic acidosis, and the presence of any of a number of comorbid illnesses (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.[302] 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.[304]

The use of antacids and histamine type 2 blockers that raise the gastric pH has been shown to increase stomach colonization with aerobic gram-negative rods.[305] Whether this leads to an increase in nosocomial pneumonia remains controversial.[42,43] The percentage of patients with VAP caused by organisms initially found in the stomach ranges from 0% to 55%.[305]

Aerobic gram-negative bacilli cause approximately 50% to 60% of cases of nosocomial pneumonia, with members of the family Enterobacteriaceae (*K. pneumoniae, Escherichia coli, Serratia marcescens, Acinetobacter* species, *Enterobacter* species) and *Pseudomonas* species accounting for the majority of these.[81] 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 among institutions, and occasionally among units within an institution.[302] 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 strains now are major pathogens in this setting.[81,85] In contrast to their prominent role in CAP, *S. pneumoniae* and *H. influenzae* together cause only about 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 hospital-acquired pneumonia, but the available data indicate that the general distributions of aerobic pathogens are relatively comparable, although there is an increase in the relative prevalence of gram-negative pathogens in patients with VAP, particularly nonenteric gram-negative bacilli.[81,306] 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 hospital-acquired pneumonia.[293] One study performed in the early 1970s at a Veterans Administration hospital with bacteriologic analysis in a research laboratory documented anaerobes in up to 35% of cases of nosocomial pneumonia, and a more recent study identified anaerobes in conjunctions with aerobic microbiota in 23% of patients with VAP.[307,308] 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. In addition, the respiratory viruses including rhinoviruses, influenza, parainfluenza, adenovirus, and RSV can cause sporadic nosocomial pneumonia and occasional institutional outbreaks.[309] There has been the recognition that the Herpesviridae herpes simplex virus and CMV can reactivate and be identified in patients with severe VAP or ARDS. The significance of this reactivation remains uncertain at this time.[302]

Consensus guidelines have been established concerning the risks, etiologies, diagnostic workup and therapies for nosocomial pneumonia and VAP. A more in-depth review will be found in Chapter 301.

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 and the chemotherapy for 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 occur in the compromised host. A large number of bacterial, fungal, viral, and noninfectious etiologies must be considered. A review of the topic is found in Chapters 305 to 308.

MANAGEMENT AND THERAPY OF PNEUMONIA

The first decision confronting the clinician is whether the patient 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 obtained in patients considered ill enough to be considered for hospitalization.[310]

The next decisions are whether the patient is to be hospitalized, and if hospitalized whether the patient needs admission to an ICU, both of which have consequences as to the level of treatment, the cost of care, and potential complications. 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.[256,311,312] Numerous severity assessment tools have now been developed to identify patients with more severe disease who require hospitalization or ICU admission.[249,259–264] 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).[249] 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–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 the ICU. The PORT score or PSI has been validated and widely endorsed.[95,313,314] 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.[312] A limitation of the PSI system is its relative complexity, and several alternative scoring systems have been developed that use more readily obtainable parameters. These include the CURB score, the CURB-65 score, and the CRB-65 score.[259–261] The CURB score was formulated from the British Thoracic Society (BTS) study and uses four clinical parameters, which include new onset of confusion, urea >7 mmol/L, respiratory rate >30 breaths/min, and systolic blood pressure <90 mm Hg or diastolic blood pressure <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 >65 years to the system, with the presence of more than three parameters leading to prediction of increased mortality; and CRB-65 modified this index to eliminate inclusion of blood urea determination, making the index laboratory free and with the patient assessment done completely at the bedside.

Several comparative trials have examined the various severity-assessment indices and assessed their usefulness.[315] These trials have indicated 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 illness severity scores for the assessment of patients with CAP.[95,310] The CRB-65, which 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.[316] 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 indices excluded patients who were HIV infected or otherwise immunocompromised, or who had recently been hospitalized. There have been several studies on the usefulness of these indices in patients with HCAP that indicate that they can be used for such patients who are not immunocompromised,[317,318] but the data are still very limited for HCAP and none are applicable for immunocompromised patients.

The PSI, CURB-65, and CRB-65 indices all predict the risk of mortality due to CAP, and not the appropriate level of inpatient admission 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 SCAP score, the SMART-COP score, and the REA-ICU index, and the use of the admission serum lactate level in conjunction with the CURB-65 score.[261,263,264,319] In addition, the IDSA/ATS guideline has recommended major and minor criteria to define patients who should be admitted directly to an ICU; these have been independently validated.[95,320] The major criteria are either septic shock necessitating vasopressor support or acute respiratory failure for which invasive mechanical ventilation is required. The presence of three of the following minor criteria also is indicative of the need for ICU care: increased respiratory rate ≥30 breaths/min, low Pao_2/fraction of inspired oxygen ratio (≤250), multilobar infiltrates, confusion or disorientation, uremia (blood urea nitrogen [BUN] 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), and hypotension for which aggressive fluid resuscitation is required. Limited data suggest that these newer scoring systems have better discriminatory power to assess the need for ICU care.[321] Still, the complexity of these additional scoring systems limits their present use, although they should be of value if they can be incorporated into diagnostic/therapeutic algorithms within electronic medical record systems. 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 for pneumonia. In reducing the microbial burden, antimicrobial therapy can reduce the duration of illness, risk of complications, and mortality rate. If diagnostic studies, as described previously, yield a likely cause, then specific narrow-spectrum agents can be used. However, for most patients a specific diagnosis cannot be established with certainty before 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 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.[322] One agent, daptomycin, has been shown to bind to pulmonary surfactant, thereby decreasing its efficacy in treating pneumonia.[323]

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 approximately 40% to 50% of the dosing interval for an optimal outcome.[324,325] Parenteral administration of aminoglycosides will lead to low concentrations in bronchial fluids when given using traditional dosing schedules, and high serum peak levels of at least 6 μg/mL for gentamicin or tobramycin and 24 μg/mL from amikacin are needed for successful outcomes in treating gram-negative pneumonia.[326] However, as aminoglycosides show concentration-dependent killing with a significant postantibiotic effect, improved clinical outcomes can be achieved with use of pharmacodynamic modeling to optimize dosing.[324,327] A retrospective pharmacodynamic and 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 ≥400, and indicates that optimal dosing should target a vancomycin trough level of 15 to 20 μg/mL.[328,329] Unfortunately, even this high level of vancomycin therapy may not be effective in treating strains of *S. aureus* that have MICs ≥2 μg/mL.[330]

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 Diseases Society have published guidelines for management of CAP, and the IDSA and ATS have published joint guidelines on managing hospital-acquired pneumonia, VAP, and HCAP in adults.[a]

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 and for HCAP is reviewed in Tables 67.5 and 67.6. Refer to Chapter 301 for recommendations for empirical management of hospital-acquired pneumonia.

For a patient who does not require hospitalization and for whom no clear distinction between typical (i.e., pneumococcal) and atypical

[a]References 85, 95, 181, 310, 331, 332.

TABLE 67.5 Guide to Empirical Choice of Antimicrobial Agent for Treating Adult Patients With Community-Acquired Pneumonia (CAP) or Health Care–Acquired Pneumonia (HCAP)

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 or CA-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)

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.
[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 2 times/day), erythromycin (250–500 mg 4 times/day).
[e]High-dose amoxicillin (1 g, 3 times/day), high-dose amoxicillin-clavulanate (2 g, 2 times/day), cefpodoxime (200 mg, 2 times/day) or cefuroxime (500 mg, 2 times/day).
[f]Vancomycin dosing should target a vancomycin trough level of 15 to 20 μg/mL; linezolid, 600 mg 2 times/day.
[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 CAP in the ICU, coverage for *S. pneumoniae* and *Legionella* species must always be considered.
[i]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 *Haemophilus influenzae* infections. They may be preferred when there is concern for relatively unusual CAP pathogens, such as *Pseudomonas 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 5–7 mg/kg IV with trough target <2 μg/mL, and 15–20 mg/kg IV for amikacin with trough target <4 μg/mL.
[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.
CA-MRSA, Community-associated methicilllin-resistant *Staphylococcus aureus*; *CAP,* community-acquired pneumonia; *COPD,* chronic obstructive pulmonary disease.
Modified from Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, 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.*

(e.g., 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, and residence in a long-term care facility are predictive of the presence of resistance to β-lactams, macrolides, and fluoroquinolones.[333–335] Where risk of drug-resistant *S. pneumoniae* is low, oral β-lactam agents (high-dose amoxicillin, amoxicillin-clavulanic acid, cefuroxime axetil), azalides and 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 a concern of an increasing incidence of resistance to both of these agents in strains of pneumococci.[95,310] Increased resistance to the azalide-macrolide agents due to blockage of the ribosomal binding area encoded by the *erm* (B) gene is also becoming a problem in *S. pneumoniae,* and therapeutic failures have been noted.[336] It has been suggested that azalide-macrolide agents may be used as long as the high-level resistance rate in *S. pneumoniae* in the community is less than 25%; however, analysis has suggested that use of this cutoff could be associated with increased morbidity and mortality in patients with pneumococcal disease.[337]

For patients with an increased risk for poor outcome because of age or underlying disease, or in whom the risk for infection with resistant pneumococci exists because of prior antibiotic use, the respiratory tract quinolones are the agents most likely to be effective. They currently are active against over 99% of strains of *S. pneumoniae* including penicillin-resistant strains, and they have the added benefit of activity against atypical agents. However, extensive use of these agents has led to increased

TABLE 67.6 Guide to Empirical Choice of Antimicrobial Agent for Treating Children With Community-Acquired Pneumonia (CAP)

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)
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
Inpatient (All Ages)	
***Fully Immunized Against* Streptococcus Pneumoniae *and* Haemophilus 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

Modified from Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, 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.*

antibiotic resistance.[338] Combination therapy with 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 with decreased mortality in adult patients with CAP compared with β-lactam monotherapy.[339,340] One hypothesis is that the immunomodulatory effects of macrolides may contribute to this effect, and the benefit may be more pronounced when macrolides are given before a β-lactam agent.[40,41,341] However, the relative benefit of β-lactam–macrolide combination therapy versus a β-lactam alone has been low or inapparent in randomized controlled trials in adults and children in which guideline-concordant therapy was addressed, using potentially more relevant clinical end points such as clinical stability or hospital length of stay.[342–347] The potential benefit of combination therapy with azithromycin is also counterbalanced by a small increased risk of sudden death due to cardiovascular events in individuals with preexisting cardiovascular risk factors.[348–350] Overall, at this time our choice for most individuals would be azithromycin plus a β-lactam (ceftriaxone or cefotaxime) except in patients at high risk of cardiovascular disease, in whom a respiratory fluoroquinolone seems preferable. If there are factors that suggest a specific cause, or if 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 in patients who have severe necrotizing pneumonia during an influenza outbreak, even though *S. pneumoniae* is still the major etiologic agent.[63] Agents with activity against MRSA should be used 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.[332,351] A prospective controlled trial comparing linezolid and vancomycin with hospital-acquired pneumonia or HCAP due to MRSA found a better initial clinical outcome for patients treated with linezolid, but no difference in mortality at 60 days.[352] 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.[353] Should the patient be found to have methicillin-susceptible *S. aureus* pneumonia, treatment with nafcillin or oxacillin is preferred. There are no current clinical efficacy data on the use of trimethoprim-sulfamethoxazole, fluoroquinolones, doxycycline, or tigecycline for treatment of staphylococcal pneumonia.

If 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 have suggested that targeted anaerobic coverage is not required for the majority of cases of CAP.[95]

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. Where 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 a 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 of initially inappropriate therapy.[354–357] 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 with in vitro activity against the presumed organisms is being given. 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* species, 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. If *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. New agents, such as ceftazidime-avibactam, that are active against ceftazidime-resistant isolates of *P. aeruginosa* have now been approved, although there are limited data available on their clinical efficacy.[358]

Timing of Antibiotics

In 1997, a retrospective review of over 14,000 Medicare patient hospitalizations suggested that antibiotic therapy given within 8 hours of presentation was associated with decreased mortality.[359] A second retrospective study of similar design in 2004 showed that antibiotics given within 4 hours of presentation resulted in lower mortality.[360] Neither study corrected for pneumonia etiology nor 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.[361–363] This hospital performance standard has subsequently been eliminated. Still, there is clear evidence that delays in antibiotic therapy can affect the outcome of patients with both pneumonia and sepsis.[340,364] The IDSA/ATS guidelines currently recommend that antibiotic therapy for pneumonia should be started as soon as the diagnosis is considered likely.[95]

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.[365] 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 (Table 67.7).[366] 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 at least a 50% reduction in CRP and determination of procalcitonin levels have been suggested as additional measures to define clinical stability, but therapeutic effectiveness and cost-effectiveness of using these approaches has not been carefully assessed.[180,367,368] Overall, once stability is achieved, clinical relapses serious enough to warrant ICU care occur less than 1% of the time.

Oral antibiotic therapy is safe after clinical stability has been reached, even in patients with severe CAP.[369–371] There is no clear usefulness for observing a patient within the hospital after a switch to oral therapy.[372] However, it is important to recognize that discharging patients before stability has been reached may lead to increased rehospitalization and mortality.[373,374] 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, are well controlled, use the same antibiotic and dosing schedule, and vary only the duration of therapy. However, these few studies have found that durations of less than 7 days and as short as 3 days of azithromycin are just as effective as longer durations of therapy for mild-to-moderate CAP.[375–377] With age, presence of underlying comorbidities including immune compromise, and more virulent pathogens, clinical stability may be delayed, and 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.[95] 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.[310] Longer therapy should be considered for patients who have high severity disease, bacteremic *S. aureus* pneumonia, or cavitary disease. The Pediatric Infectious Diseases 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.[332]

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.[158,342,344,378–381] The use of inpatient critical pathways (care bundles) based on clinical practice guidelines can reduce inpatient length of stay and 30-day inpatient mortality without increasing adverse effects.[313,382–384]

Once the patient has been 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.[374,385]

Adjunctive Therapy

A robust inflammatory response to an invading pathogen can lead to a potentially worse outcome in pneumonia, and the use of antiinflammatory agents could have potential benefits as demonstrated with the improved outcome with the addition of corticosteroid therapy for *Pneumocystis* pneumonia. Several randomized controlled trials have now investigated the efficacy of corticosteroid therapy for CAP using differing dosages and agents. To date, steroids appear to shorten the time to clinical stability and overall inpatient length of stay by 1 day; but are also associated with an increase in hyperglycemia and subsequent rehospitalization.[386–389] Statins also possess antiinflammatory properties, and their impact on CAP has been assessed in observational studies. Although there was initial suggestive evidence of benefit, those studies were not been randomized and did not control for other potentially important variables such as underlying health or socioeconomic status.[390] More recent studies have found no impact of recent statin use on clinical outcomes in CAP.[391,392] 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.[393]

TABLE 67.7 Evidence of Clinical Stability or Improvement

Temperature ≤37.8°C
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

Modified from Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, 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, Bartlett JG, Campbell GD, Dean NC, 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.*

PREVENTION OF PNEUMONIA

Vaccinations 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.[394,395] 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.[396]

A 23-valent pneumococcal polysaccharide and both 7-valent and 13-valent pneumococcal conjugate vaccines are licensed in the United States. Good clinical data show that these vaccines provide protection against bacteremia and invasive pneumococcal disease, and the introduction of the pneumococcal vaccine into the US childhood immunization program has been associated with a notable reduction in pneumonia incidence in all age groups, indicating a ("herd") community effect.[227] Limited data now show a direct effect of adult pneumococcal immunization in decreasing pneumonia incidence.[397,398] Both the 23-valent pneumococcal polysaccharide and 13-valent pneumococcal conjugate vaccines have now been approved for use in adults older than 50 years, and pneumococcal vaccine is recommended for patients older than 65 and those who have recovered from CAP. The efficacy and sequence of administration of these vaccines are discussed further in Chapter 199.

Active smoking is a clear risk factor for bacterial pneumonia, and promotion of smoking cessation should be a component of pneumonia prevention.[66,399,400]

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68 Pleural Effusion and Empyema

Mark Parta

SHORT VIEW SUMMARY

Physiology

- The small volume of fluid in the pleural space at baseline increases with infection or other inflammatory conditions.
- Multiple cytokines and factors contribute to this change, including vascular endothelial growth factor, interleukin-1α and interleukin-1β, tumor necrosis factor-α, and interleukin-6.
- These factors should be taken into consideration because of the increasing therapeutic use of drugs/agents that antagonize them.
- Coagulation and fibrin clots contribute to the evolution of effusions into loculated collections of material that become progressively more resistant to medical therapies.

Diagnosis

- Community-acquired pneumonia is the most common predisposing condition to pleural infection. Symptoms in addition to those related to the pneumonia may include chest pain and splinting on the affected side, but symptoms and signs are both insensitive and nonspecific. Conventional chest x-rays may be insensitive for effusions, which occur in >40% of cases of community-acquired pneumonia.
- Computed tomography scans and ultrasound may enhance detection of fluid, but only ultrasound reliably detects the organization of an effusion by septation/loculation. Ultrasound improves sampling accuracy.
- Only pleural fluid sampling reliably characterizes effusions. Fluid should be stained and cultured for bacteria, fungi, and mycobacteria, and studied for cell content, pH, and chemistry (lactate dehydrogenase [LDH], glucose, and protein).
- The clinical context should dictate additional testing, such as pneumococcal antigen in the context of lobar pneumonia, molecular assays for viruses or mycobacteria, or pleural biopsy for tuberculosis. Surrogate markers such as adenosine deaminase have a role in certain settings.

Fluid Analysis

- Fluids are divided into transudates or exudates on the basis of chemistries. Transudates are characteristic of noninfectious processes such as congestive heart failure, but occasionally occur early in the course of parapneumonic effusion and may respond to medical therapy alone.
- Exudates, with high protein and LDH content, are more likely to require drainage by tube thoracostomy early. Tuberculosis is the exception, since most tuberculous effusion is exudative but resolves spontaneously even without treatment. Low pH is a strong predictor of the need for aggressive drainage of a parapneumonic effusion and requires submission for testing in a closed syringe like a blood gas.
- Empyema is not characterized by chemistry, but by appearance (purulence, pus) and/or positive microbiologic studies.

Microbiology

- Infecting agents in pleural fluid are often associated with pneumonia. Tuberculous pleurisy is common when tuberculosis is prevalent. *Streptococcus pneumoniae* remains an important cause of community-acquired bacterial pneumonia and pleural disease. Members of the *Streptococcus anginosus* group are important empyema pathogens but infrequent causes of pneumonia.
- In adults, especially older adults, pleural infection is often the result of aspiration or obstruction related to malignancy. In that context, methicillin-resistant *Staphylococcus aureus,* gram-negative organisms, and anaerobic upper aerodigestive tract organisms predominate.
- Fungal empyema is most often caused by *Candida,* and *Candida* recovered from a pleural effusion suggests disruption of the gastrointestinal tract, often the esophagus, as a source.

Management

- Thoracentesis is diagnostic and rarely therapeutic. Effusions that require drainage almost always require placement of a chest tube (tube thoracostomy).
- Antimicrobial therapy should be appropriate to the setting, especially when organisms such as methicillin-resistant *S. aureus,* gram-negative organisms, and anaerobes are potential pathogens.
- Although fibrinolytic therapy, usually recombinant tissue plasminogen activator combined with recombinant DNase, may aid in achieving drainage, the settings in which it contributes to clinical outcomes are poorly defined.
- Medical and video-assisted surgical thoracoscopy are intermediate-stage interventions that allow for directed evacuation of infected space without full surgical intervention by thoracotomy. These are appropriate when fluid is no longer free flowing or the pH is <7.3, but at some poorly defined stage of pleural thickening, operative management by thoracotomy is necessary.
- Chronic empyema requires thoracoscopic treatment or thoracotomy and is a high-morbidity and high-mortality condition. Additional surgical measures are often necessary, especially when bronchopleural fistula is present.

Thoracic empyemas appear in the Hippocratic corpus.[1] In the 16th century, the famous essayist and physician Michel de Montaigne wrote in his essay on the fear of death, "I omit to speake of agues and pleurisies…," recognizing their routine role in mortality.[2] In the early 20th century, one of medicine's most famous practitioners, Sir William Osler, died of complications of empyema.[3]

PHYSIOLOGY AND STAGING

Three factors control the flow of the small volume of fluid that lubricates the pleural space. The pulse of fluid (hydrostatic pressure) is accompanied by osmotic pressure between the vessels in the parietal pleura and the pleural space. The outflow of fluid is in a dependent direction through lymphatic stomata in the lower parietal pleura. The pleura itself consists of collagen and elastic fibers that contain interspersed mesothelial cells. These are metabolically active and mediate some portion of the inflammatory response, as well as provide part of the barrier function of the pleura.[4] The quantity of fluid in the pleural space, measured by in vivo pleural lavage, is 0.26 ± 0.1 mL/kg whole body weight, with 1.7×10^6 white blood cells/mL. Macrophages are the predominant cell (75%), followed by lymphocytes (23%) and mesothelial cells (1%). Smokers have a small increase in neutrophils.[5] In response to infection or injury, the fluid content of the space increases. Uncomplicated effusions usually

respond to measures directed at their cause, for instance, treatment of a pneumonia accompanied by a parapneumonic effusion. Complicated effusions represent a middle point, with the development of fibrinous material over time that will cause septations and loculation of the fluid if the cause is not successfully addressed. Complicated effusions and empyema are likely to require drainage and therapy directed at the pleural complication itself.[6]

Multiple staging systems have been developed to characterize the evolution of pleural disease. Pleural fluid is a transudate when it is primarily influenced by changes in hydrostatic pressure in heart failure and fluid overload states such as renal failure or cirrhosis. Exudates are characteristic of effusions associated with cancer, infection, and many noninfectious causes, as further discussed in "Fluid Analysis" (see later). A three-stage division of the evolution of pleural disease is practical and can be integrated into most of the medical literature, as seen in British Thoracic Society (BTS) and American Association for Thoracic Surgery (AATS) guidelines, which reference an American Thoracic Society statement from 1962.[7–9] The first stage (exudative, stage I [AATS]; simple parapneumonic effusion [BTS]) shows clear fluid with a low cell count and reexpandable lung. The pH is >7.2, lactate dehydrogenase (LDH) is <1000 IU/L, and glucose is >2.2 mmol/L. The second stage is fibrinopurulent (AATS) or complicated parapneumonic effusion (BTS), with high cell count, fibrin deposition, and biochemical parameters of pH <7.2, LDH >1000 IU/L, and glucose <2.2 mmol/L, and there may be a positive culture. The third phase (organized [AATS]; empyema [BTS]) is frankly purulent fluid, which is thick and may present with trapped lung and membranes on the pleural surface. It is important to note that empyema is still defined as fluid that is purulent or has positive microbiologic studies. For parapneumonic effusion, the risk for outcome associated with pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry yielded a four-category assessment as documented in a 2000 statement from the American College of Chest Physicians.[10] A classification from Light includes seven stages.[11]

The physiology of infected pleura changes as infective organisms interact with the immune system. Staphylococcal peptidoglycan induces the production of β-defensins in a murine model, and signaling cascade antagonists interfere with this.[12] Vascular endothelial growth factor (VEGF) increases permeability and fluid in the pleural space.[13] The consequence of VEGF antagonism in clinical practice confirms the importance of this mechanism. Levels of VEGF are higher in parapneumonic effusions than in those caused by congestive heart failure (CHF). Experiments with mesothelial monolayers show that *Staphylococcus aureus* causes a response similar to that induced by recombinant VEGF, with a decrease in electrical resistance across the cells and protein leaks across the monolayers.[14]

The evolution of infected effusions may differ with the infecting organism, the difference between bacterial and mycobacterial disease being illustrative. Bacille Calmette-Guérin, in an in vitro model, decreases the tight junction between cells by downregulating β-catenin, an adherens junction protein. This leads to increased permeability due to VEGF production and then the protein influx characteristic of exudative effusions.[15] Inflammatory mediators, such as cytokines, are produced by mesothelial cells and pleural macrophages. In 70 patients with various etiologies of effusion, interleukin (IL)-1β was higher in parapneumonic than malignant effusion, and was produced by pleural macrophages in response to lipopolysaccharide. Interferon-γ in particular is elevated in the pleural fluid of patients with tuberculosis.[16] Variations in these cytokine profiles have led to attempts to use IL-1α, IL-6, and tumor necrosis factor-α (TNF-α) as diagnostic tools that would differentiate transudates from exudates. IL-6 differentiated exudates (high levels) from transudates and was significantly higher in tuberculous than malignant or parapneumonic effusions.[17] Some of the differences between nonspecific effusions and those due to tuberculosis are attributable to the known role of $CD4^+$ lymphocytes in the immunology of tuberculosis, as discussed in Chapter 251.[18]

Cell wall constituents of *Mycobacterium tuberculosis,* such as the protein-peptidoglycan complex and lipoarabinomannan, cause the release of TNF-α from pleural fluid mononuclear cells in a dose-dependent manner, which may account for the classical manifestations of tuberculous pleurisy, such as fever, an exudative effusion, and tissue necrosis.[19] Cytokine changes drive the accumulation of neutrophils. TNF-α induces neutrophil chemotactic activity driven by IL-8, which is higher in empyema than in nonpurulent effusions of any etiology. TNF-α levels and activity diverge, though, with high levels in both empyema and tuberculous fluid, but increased bioactivity only in empyema.[20]

An additional two components of progression in effusion and empyema are coagulation and fibrosis. In animal models, blocking transforming growth factor-β with an antibody decreases purulence and fibrosis.[21] A loculated effusion with fibrous septations is linked to procoagulant activity and decreased fibrinolytic activity in exudates, mediated by mesothelial cells. This important in vitro observation supported clinical trials of fibrinolytics in the treatment of pleural effusion, as delineated later.[22]

NONINFECTIOUS EFFUSION AND EMPYEMA

Pleural effusion can be caused by myriad noninfectious processes. In some of these, there are sufficient descriptions of the likelihood and character of the effusion to increase diagnostic certainty. General states of fluid overload, such as CHF, renal failure, and cirrhosis, are common causes of effusion.[23] Inflammatory noninfectious diseases such as rheumatoid arthritis, systemic lupus erythematosus, and pancreatitis are important differential considerations. Cancers, generally secondary but occasionally primary in the pleura, with mesothelioma prominent among them, are common causes of exudative effusion.[24] Tunneled indwelling pleural catheters (PleurX Drainage System) increasingly are used for chronic drainage in malignant effusions from solid tumors or hematologic disease. These of necessity carry an infection risk, reported as 7.7% in hematologic malignancies and 3.7% in other malignant effusions.[25] The report of longer survival in melanoma patients whose effusions become infected in this context is of dubious significance.[26] Thoracic surgical procedures, from cardiac surgery to lung transplantation, are usually followed by an accumulation of exudative pleural fluid, which decreases more rapidly after cardiothoracic surgery than lung transplantation.[27–29] Elevated neutrophil counts are the most sensitive and specific indicators of infection.[30] Drugs may be associated with effusion, with or without parenchymal involvement. Of note, immune checkpoint inhibitors, while associated with pneumonitis, are rarely if ever the causes of pleural effusion. Thus an effusion in the context of these therapies requires investigation for potential infectious causes.[31] Distinguishing characteristics of some noninfectious causes of pleural effusion are presented in Table 68.1.

The epidemiology of infectious pleural effusion is influenced by the rigor of attempts to detect effusions, the era reported, the age of the population studied, and the prevalence of tuberculosis and other endemic diseases. The outcome of bacterial pleural disease is heavily influenced by the success of treating an associated bacterial pneumonia. In a pediatric hospital in the United States, temporal trends from before and through the initial years of the antibiotic era show a drop in empyema from 1934 to 1958, with decreases in cases caused by *Haemophilus influenzae,* streptococci, and pneumococci but a rise in *S. aureus* in later years, coincident with an influenza epidemic.[32] In adults from 1933 to 1972 (a survey of selective, noncontinuous sample years), a similar decline in pneumococcal disease occurred, and the same increase in *S. aureus* was seen in 1955, with a decrease through 1965. As disease caused by antibiotic-susceptible organisms decreased, mortality associated with empyema increased, as did the age of the population affected.[33] Hospital-acquired disease, described in a separate report on duration of hospitalization, had already shown a trend to an increase in disease caused by gram-negative bacilli, *S. aureus,* and enterococci. Improvements in antibiotic therapy may have been responsible for shorter hospitalizations in the later years compared to those in the preantibiotic era.[34] Later influenza epidemics may have had a different spectrum of bacterial complications. In children, *Streptococcus pneumoniae* and *Streptococcus pyogenes* were the most frequent causes of secondary bacterial pneumonia in the 2009 influenza A(H1N1) epidemic.[35]

In a Spanish report of empyema from 1984 to 1990, adults had underlying disease in 82% of cases, including alcoholism, malignancy, and diabetes mellitus.[36] Anaerobic bacterial disease is increased in this population as a consequence of aspiration and obstruction. In a

TABLE 68.1 Noninfectious Pleural Disease

	PLEURAL DISEASE FREQUENCY	FLUID CHARACTERISTIC	COMMENT	REFERENCE
Inflammatory Diseases				
Sarcoidosis	Rare	Serous exudate by LDH/protein, paucicellular	Consider other causes; diagnosis by pleural biopsy	218
Rheumatoid arthritis	3%–5%	Exudative, low glucose, sometimes chylous	Does not necessarily correlate with joint disease	219, 220
Adult-onset Still disease	17%–53%, literature summary 21%	Sterile exudate, neutrophil predominant	Arthralgia inevitably present	221, 222
Sjögren syndrome	Rare	Exudate but normal pH, glucose, and low ADA	Secondary most common; concern about concomitant lymphoma	223, 224
Granulomatosis with polyangiitis	Rare but summary 12.4%	PMN leukocytes predominant exudate		225, 226
Eosinophilic granulomatosis with polyangiitis	17.6%	Bloody effusion, high eosinophil count	Disease-associated heart failure may contribute	227, 228
Systemic lupus erythematosus	5% at presentation, 30%–50% during the course of disease	High protein exudate, higher glucose/lower LDH than RA, neutrophils early	Likely to be symptomatic, and complement/ANA on effusion not diagnostic	229, 230
Behçet syndrome	Rare (5%) but in 70% of cases with lung disease	Transudate and chylothorax	Presumed relation to thrombosis of central veins	231
TAFRO syndrome	CR, almost all from Japan	NR	IL-2 and IL-6 implicated in pathogenesis	232
Other				
Eosinophilic effusion	Cancer > PPE > tuberculosis	Eosinophils >10%	Inverse relation to likelihood of malignancy	233
Trauma	Rib fracture in 71%, pulmonary contusion in 43%	Hemothorax 39%	Retained hemothorax (higher with medical vs. surgical management) and late effusions risk for empyema	234, 235
Pulmonary embolism	48%	Small	Ipsilateral to embolus, predicted by infarction and CRP	236, 237
Post–cardiac injury syndrome	56%–92%	70% bloody exudate, cells transition from neutrophils to mononuclear cells	Usually with ipsilateral pneumonitis, usually left sided but can be bilateral	27, 28
Radiation therapy	29.1%; symptoms associated with whole lung volume receiving ≥5 Gy	Free flowing early, loculated late	Always associated with pneumonitis	238, 239
Rounded atelectasis	23%	Exudative	Frequently with asbestos-related pleural thickening	240
Superior vena cava syndrome	Rare	Transudate when result	Effusion cause or result of SVC syndrome	241, 242
Hematopoietic stem cell transplant	9.9%	56% exudative	Engraftment syndrome early; GVHD late	243
Pancreatitis	22%–29%	Hemorrhagic; high LDH and protein, amylase Neutrophil predominance	Late or persistent effusion suggests fistula	244
Meigs syndrome	Defining	Exudative	Responsive to removal of tumor	245
Drugs				
Daptomycin	66.7%	NR, bilateral lung infiltrates, bronchial lavage >25% eosinophils	Not clearly related to dose or duration	246
Dasatinib and other tyrosine kinase inhibitors	35%	Usually bilateral, hemorrhagic or chylous, asymptomatic, lymphocyte predominant	Dose and frequency dependent	247

ADA, Adenosine deaminase; *ANA,* antinuclear antibodies; *CR,* case report; *CRP,* C-reactive protein; *GVHD,* graft-versus-host disease; *IL,* interleukin; *LDH,* lactate dehydrogenase; *NR,* not reported; *PMN,* polymorphonuclear neutrophil; *PPE,* parapneumonic effusion; *RA,* rheumatoid arthritis; *SVC,* superior vena cava; *TAFRO, t*hrombocytopenia, *a*nasarca, *f*ever, *r*enal failure or *r*eticulin fibrosis, and *o*rganomegaly.

more restricted referral center for cardiothoracic disease in the United Kingdom (predominantly male, median age 53 years), most empyema was community acquired and the microbiology was diverse, with 16.3% streptococci, 15.5% staphylococci, and gram-negative, anaerobic, pseudomonad, mycobacterial, and polymicrobial infections in lesser proportions. Tuberculosis still caused 9.1% of cases.[37] Other reports with geographic restrictions are informative. Decreases in tuberculosis in Europe and the United States have not occurred to the same extent elsewhere. Tuberculous effusion accounted for 49 of 100 effusions in a series from Malaysia in 1991.[38] In East Asia, despite high rates of *Klebsiella pneumoniae* pleural infection, the majority of empyema is not caused by hyperviscous serotypes.[39]

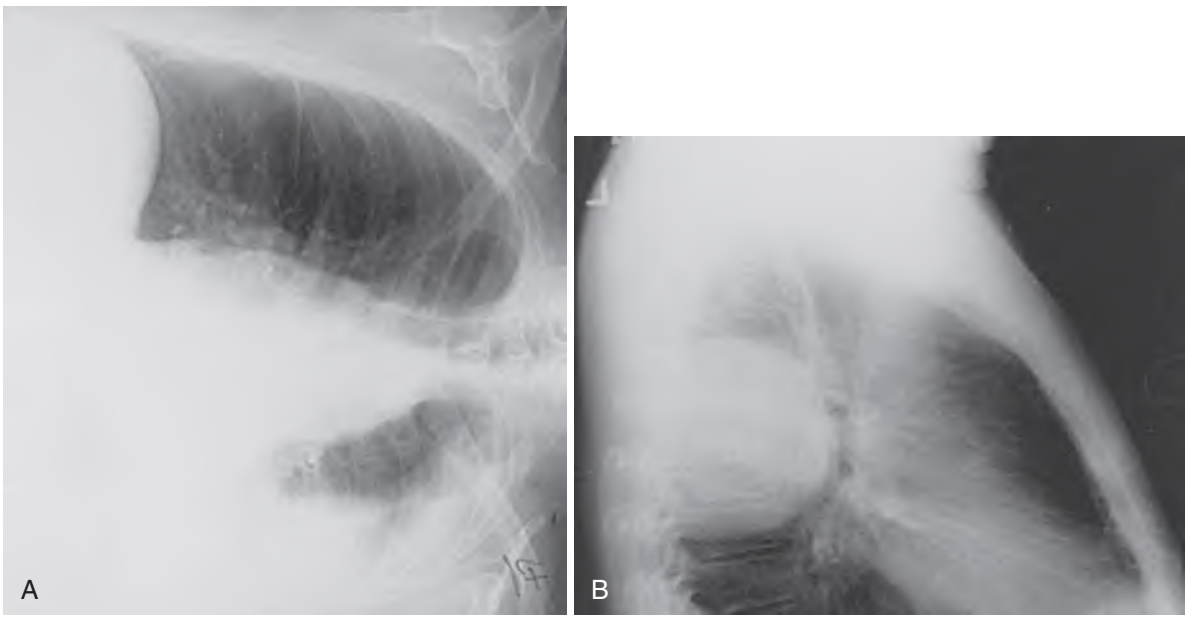

FIG. 68.1 Pleural effusions. (A) Empyema fluid is seen layering out along the dependent chest wall of a patient with left lower lobe pneumonia (left lateral decubitus film). (B) D-shaped mass representing a loculated empyema at the site of a former right upper lobectomy.

OUTCOMES OF EFFUSION AND EMPYEMA

The consequences of an infected pleural effusion depend on the population, on the infection, and, critically, on the vigor with which the physician makes the diagnosis and chooses the right therapy. Most tuberculous effusion (see below) is a low-mortality disease and remits even without therapy, but treatment decreases the likelihood of further tuberculous disease.[40] At the other end of the spectrum, postpneumonectomy empyema affects an older population with a high incidence of malignancy, so that the 5-year survival after surgical therapy was 44.5% in a series of 84 patients treated with the Clagett procedure.[41] In the UK Multicenter Intrapleural Sepsis Trial (MIST) 1, a clinical risk score was developed with levels of low (0–2), medium (3–4), and high risk (5–7). The derived score accurately predicted death at 3 months, but in a validation cohort from MIST 2 the significance of the medium score was lost.[42]

Early diagnosis and therapy are of paramount importance, yet assessment and management often are not adequate.[43,44] A retrospective analysis of prognostic factors over a 9-year period in 158 patients from Denmark (mean age 63 years) found, with an overall mortality of 27%, that nosocomial infection, predisposing conditions, and insufficient initial antimicrobial therapy correlated with poor outcome. Only 36% of patients were appropriately assessed, and the authors commented on the poor adherence to recommended diagnostic approaches in both emergency rooms and internal medicine wards.[45] Three studies of note examined the outcomes and factors affecting morbidity and mortality from empyema or pleural infection. Outcome was related to delays in drainage, with patients with the most severe disease (requiring decortication) suffering the highest mortality when the procedure was delayed.[46] A nonblinded study of 179 patients established the frequency of the need for decortication and the results of less aggressive therapy. Ninety percent of those deemed eligible for thoracocentesis alone were cured, but chest tube therapy alone (closed thoracostomy) was successful in only 62% and had a mortality of 11% in 90 patients, with second procedures needed in 24 cases. Primary or secondary decortication had a cure rate of 88% and mortality of 1.3% in another study with 76 patients.[47] Finally, risk stratification for the need for surgery was studied in 85 patients who received drainage and intrapleural fibrinolytics. There were medical failures (need to proceed to surgery) in 15%, and the absence of purulence predicted medical success but the presence of purulence did not predict failure. The overall survival was 86%.[48]

MICROBIOLOGY

Tuberculosis

The pleural manifestations of tuberculosis have been studied throughout the modern era. In the United States, pleural disease was found to be secondary only to lymphadenitis in extrapulmonary cases from 1993 to 2006. Because of its remitting nature and the difficulty of microbiologic diagnosis when only pleural fluid is sampled, pleural tuberculosis in the early 20th century was not uniformly considered tuberculous disease, but was followed by pulmonary/extrapulmonary tuberculosis in 34.8% of children and 52.6% of adults in a 1912 summary of cases from 1881 to 1908.[49] At the transition from a prechemotherapeutic era to effective drug therapy, Roper and Waring clarified the role of pleural disease as the antecedent to complicated disease (pulmonary or extrapulmonary).[50] Bed rest, once standard therapy, did not decrease this rate of progression, and Falk and Stead established that drug therapy did.[40]

In an urban setting in which the demographics were not yet dominated by human immunodeficiency virus (HIV) infection, pleural disease occurred in older adults and was associated with reactivation in 19%, and comorbidities made the diagnosis difficult.[51] With further evolution of the HIV epidemic, both the breadth and adverse consequences of tuberculosis in HIV-infected persons became apparent, with pleural disease as a common manifestation.[52,53] The $CD4^+$ T-lymphocyte depletion characteristic of HIV disease has proven the perfect storm in all manifestations of tuberculosis, including pleural disease. The role and characteristics of $CD4^+$ lymphocytes in pleural effusions (Fig. 68.1) reactive to purified protein derivative have been established, and interferon-γ, a product of activated T cells, induces the expression of mesothelial cell–derived monocyte attractants (as does bacille Calmette-Guérin).[54–57] The clinical consequences of ineffective $CD4^+$ cell-mediated defense has been shown in Rwanda, where pleural effusion was significantly more frequent in HIV-infected than in HIV-uninfected persons (43% vs. 9%). This may be true with higher $CD4^+$ T-cell counts, and appears in association with weight loss and lower lobe parenchymal disease.[58]

The clinical features of pleural tuberculosis, whether coincident with primary pulmonary disease or the primary site of disease alone (see later), include fever, dyspnea, malaise, diaphoresis, and pain antecedent to the effusion, sometimes by months. Effusions are usually unilateral. The diagnosis of pleural tuberculosis is difficult unless multiple modalities are used, including the analysis of pleural fluid, pleural biopsy, pleural fluid and pleural tissue culture, and sputum culture. Pleural fluid specificity can be maximized on exudative effusions with the parameters

of lymphocytes >80%, protein >5 g/dL, and adenosine deaminase (ADA) >45 U/L (see later), but the sensitivity remains inadequate at 34.9%.[59]

Pleural biopsy clearly established the infectious (rather than allergic) nature of pleural disease, and the use of Cope needle biopsy in 40 patients on the Columbia service at Bellevue Hospital found necrotizing granulomas in 63% and positive cultures of pleural tissue in 55%, with a combined diagnostic yield of 80%.[60] Multiple biopsies may increase the yield (6 biopsies with a sensitivity of 100%).[61] A contemporary study from Brazil found that tissue yielded a histopathologic diagnosis in 78% of cases, pleural tissue culture in 62%, and induced sputum in 52%, emphasizing the frequent occurrence of concomitant pulmonary disease, which should be sought by sputum culture even in the patients with clinically isolated pleural disease.[62] The incidence of parenchymal disease in patients with pleuritis has been underestimated.[63] The likelihood of a positive pleural fluid culture varies with the stage of disease. Tuberculous effusions evolve from polymorphonuclear cell predominance to the more characteristic lymphocyte predominance, and the yield of culture (including sputum) in the former has been higher.[64,65] Interferon-γ production by T lymphocytes has been studied as a surrogate diagnostic, and levels are elevated in tuberculous effusions.[66] Cells responsive to the antigens targeted in commercially available interferon-γ release assays are 15 times higher in tuberculous than nontuberculous effusions.[56] However, commercial assays remain appropriate for the diagnosis of latent tuberculosis but not tuberculous disease in the pleural space. A review and meta-analysis of 14 studies concluded that they were of poor quality, with substantial variation in thresholds for positivity and pooled sensitivity and specificity of 72% and 78%, respectively.[67]

New molecular and other microbiologic assays have been studied. The microscopic observation drug susceptibility assay, recently commercialized, showed greater sensitivity than culture on standard solid media. The study results are confounded by disproportionate loss of sensitivity with decontamination, which process may be of questionable utility on a sterile specimen such as pleural fluid.[68]

Of the surrogate markers studied and of potential clinical utility, by sheer volume of literature ADA would require a chapter by itself. This only serves to emphasize the common problem of a continuous variable used to determine a categorical outcome. The test is inexpensive and widely available. In circumstances in which tuberculosis is prevalent and the differential diagnosis is principally diseases that do not routinely cause a lymphocyte-predominant exudative effusion, an ADA level above 40 U/L and a lymphocyte-to-neutrophil ratio >0.75 support the diagnosis of tuberculous effusion.[69]

The Amplified Mycobacterium Tuberculosis Direct Test (Hologic, Inc., San Diego, CA) had a sensitivity of only 36.4%, but the performance was better in neutrophilic effusions (see earlier) and those of <18 days' duration.[70] Finally, the important GeneXpert product Xpert MTB/RIF (Cepheid, Sunnyvale, CA) has been evaluated in multiple studies. The sensitivities range from 14.2% to 28.7%, but specificities are high and results are rapid, although costs are high.[71,72]

The specificity of pleural radiographic abnormalities is poor in the absence of characteristic pulmonary disease. The pulmonary abnormalities prominent by computed tomography (CT) scan of the chest include micronodules in subpleural and peribronchovascular interstitium. Interlobular septal thickening suggests the lymphatic spread characteristic of the disease.[73]

The treatment of pleural tuberculosis is the same as that of pulmonary disease. Six-month therapy with isoniazid and rifampin led to no relapses in 161 patients, even when associated with smear-negative/culture-positive pulmonary disease.[74] Corticosteroids are not indicated for the treatment of pleural disease because long-term benefit is uncertain due to many confounders.[75] Therapeutic thoracocentesis may relieve dyspnea in large effusions but is otherwise not indicated.[76]

Paradoxical responses, including unmasking or worsening pleural disease at the initiation of antiretroviral therapy, are well described in HIV/tuberculosis-coinfected patients.[77] This may also occur in HIV-negative persons, as described in 16% of isolated pleural disease cases in which effusions worsened at 2 months after the initiation of therapy, but 68% of these patients were asymptomatic.[78]

Tuberculous empyema accounts for a small proportion of cases of pleural tuberculosis but has severe consequences. It may be a chronic condition that degenerates with the development of a bronchopleural fistula or empyema necessitatis (the extension of empyema fluid through the parietal pleura and out the chest wall) (Fig. 68.2). Often the symptoms are chronic, with low-grade fever, night sweats, and weight loss. Fluid is by definition grossly purulent with high neutrophilic cell counts, acidic pH, and low glucose. Therapy is by drainage and chemotherapy.[79] Outcomes of surgical intervention vary by indication, with low morbidity associated with diagnostic procedures, but high morbidity and some mortality following complex surgical procedures such as placement of an Eloesser flap.[80,81]

FIG. 68.2 Spontaneous drainage (empyema necessitatis) from the posterior chest wall of a 55-year-old man with malignant mesothelioma and a loculated empyema. A PleurX catheter had been placed anteriorly. Culture from the draining sinus grew *Pseudomonas aeruginosa, Actinomyces odontolyticus, Granulicatella adiacens,* and *Finegoldia magna.*

Other Bacteria

Lobar pneumonia commonly is caused by *S. pneumoniae*, and so pneumococcal empyema accounted for 68.3% of cases at the Boston City Hospital in 1930. The disease was "meta-pneumonic" in that empyema occurred several days after the onset of pneumonia and progressed over a few days from turbid fluid to purulence, and the turbid and fibrinous character of the fluid impeded drainage. Bronchopleural fistula and abscess may ensue. Even with the bacteriology of the early 20th century, 25% of cases were bacteremic and these showed increased mortality.[82] A historical survey of selected years from 1935 to 1972 noted a declining but still high prevalence of pneumococcal empyema during the early penicillin era (46% decreasing to 15% from 1935 to 1957), and pneumococcal disease still accounted for 12% to 16% in the later years studied.[33] In a prospective study from 1978, vigorous assessment of 35 cases of pneumococcal pneumonia found that 57%

had parapneumonic effusions and 3 were empyemas at admission. The authors suggested that patients with effusions had pneumonia for longer periods before diagnosis and therapy.[83]

The modern literature (roughly the last 50 years) on pneumococcal empyema is dominated by pediatric studies, not addressed here in detail. In adults, 128 cases of pneumococcal empyema occurred in 1808 patients with invasive disease, and the rate increased across the periods studied (1996–2001 and 2005–2009). These years were chosen to coincide with the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), in parallel with pediatric reports that invasive disease and especially empyema had increased coincident with the introduction of the vaccine.[84,85] Additional population-specific factors contribute to the severity and character of complicated/invasive pneumococcal disease, especially HIV infection. A survey of global epidemiology, specifically addressing serotypes in complicated pneumococcal pneumonia from 1990 to 2012, supported increases in both the disease and geographic variation in serotypes responsible. The summary supported several factors as contributing to this, including better detection methods and diagnostics, and perhaps increases in invasive serotypes not targeted by PCV7.[86] However, other data demonstrate that invasive disease increased prior to the introduction of PCV7 and the increase in serotypes association with invasive potential.[87,88] With the introduction of 13-valent conjugate vaccine (PCV13), which includes many of the dominant invasive serotypes noted previously, observational evidence in patients <18 years of age did not yet support a decreased incidence of complicated parapneumonic effusion. Of vaccine serotypes, in an area of high PCV13 coverage, however, only serotype 3 persisted as a cause of empyema.[89,90]

Specific considerations in the diagnosis of pneumococcal effusion and empyema relate to the deficiencies in standard culture-based methods (sometimes associated with prior antibiotic use), and so antigen detection and molecular methods are used increasingly. In a pediatric literature review, polymerase chain reaction (PCR) and pneumococcal antigen detection in 78 empyema cases found that PCR added 17 diagnoses to 23 made by culture.[91] Pneumolysin-targeted PCR was used for specificity after 16S ribosomal DNA PCR. Latex detection using the BinaxNOW *S. pneumoniae* antigen detection test (Alere, LLC, Orlando, FL) detected 90% of the cases. A subsequent study from Spain noted that the same antigen assay on pleural fluid increased detection by 38% over culture alone and had a sensitivity of 70.6% with specificity of 93.3%.[92]

Finally, the specifics of treatment of pneumococcal pleural disease broadly follow those of the treatment of pneumococcal pneumonia in terms of antimicrobial therapy. In Spain, with a high prevalence of pneumococcus isolated from pleural fluid with elevated minimal inhibitory concentrations to penicillin from 1997 to 2008, oral penicillin nonsusceptibility decreased as PCV7 serotypes decreased, but increases in serotype 19A occurred, one of 3 serotypes (1, 3, 19A) responsible for empyema in 2008, and penicillin nonsusceptibility in 19A was 82.4%.[93]

Staphylococcus aureus remains an important pulmonary and empyema pathogen because of its virulence and drug resistance characteristics. Its prevalence waxes and wanes prominently with influenza epidemics.[94] In a report from Brazil of 332 cases of community-acquired pneumonia from 1992 to 2003, *S. aureus* (95% methicillin-susceptible) accounted for 24 cases, but empyema occurred in half. Predisposing conditions reported were skin infections, septic abortion, and a history of upper respiratory tract viral infection.[95] Empyema resulting from *S. aureus,* especially methicillin-resistant *S. aureus* (MRSA), is a critical component of health care–associated and hospital-associated empyema.[96] *Staphylococcus aureus* may complicate hemothorax secondary to trauma (late at 10 days postdrainage), but gram-negative organisms colonizing the upper respiratory tract cause empyema early (within 4 days of drainage) after pneumo- or serothorax.[97]

Other gram-positive organisms of note in large surveys are often referred to as β-hemolytic streptococci, often not otherwise specified, especially in older literature. *Streptococcus pyogenes* (group A β-hemolytic streptococcus) was prevalent in the preantibiotic era, accounting for 18% to 34% of empyema. The disease is characteristically aggressive and associated with much morbidity and mortality.[33,82]

In current taxonomy the *Streptococcus anginosus* group (formerly the *Streptococcus milleri* group), of which some members are β-hemolytic, are infrequent causes of pneumonia but are increasing as causes of pleural infection. Predisposing conditions such as diabetes mellitus and malignancy are often present in these cases, and mortality has been reported at 14%.[98–100]

Dedicated studies of infections with anaerobic organisms in the 1970s identified multiple species as contributing to pleural infection. Bartlett and Finegold found that anaerobic bacteria are characteristic of pulmonary processes and pleural complications in cases of aspiration and necrotizing pneumonitis, which may evolve to lung abscess. Anaerobic empyema was present in 17 of 43 cases reported, with only one exception associated with parenchymal disease, and 33 required open thoracotomy. Anaerobes only were present in 28 cases, with *Fusobacterium nucleatum, Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*), and other spp., and microaerophilic streptococci as the dominant species. In mixed infections, *Escherichia coli*, *S. aureus,* and *Pseudomonas aeruginosa* were present.[101] Twenty years later, the same institution reported on 37 cases (19 purely anaerobic) in which 161 isolates from 46 samples cultured anaerobically (3.5 per patient) were found. *Fusobacterium*, *Prevotella, Bacteroides,* and *Peptostreptococcus* (*P. magnus,* now often classified as *Finegoldia magna*) were the dominant species. Susceptibility data noted β-lactamase production in 33% of the isolates.[102] An analysis using a library of cloned fragments without culture studied 42 specimens from 26 patients. Among these, 43.8% had dominant anaerobic phylotypes, and 6 of 7 of these were not detected by culture; 9 of 26 cases showed discordance between molecular and culture results.[103] With the infrequent application of culture methods appropriate to anaerobic organisms and frequent lack of susceptibility testing, these results emphasize the need to consider the presence of organisms that may represent a risk of failure of treatment. For instance, resistance of *Peptostreptococcus* to metronidazole, the frequent production of β-lactamases, the general inadequacy of cephalosporins alone for the treatment of gram-negative anaerobes, and increasing rates of resistance to clindamycin should be taken into consideration.[104,105]

Other gram-positive streptococci and enterococci are less frequent pathogens in monomicrobial empyema, although they may contribute to the microbiology of polymicrobial infections when pleural disease results from aspiration and/or lung abscess. These infections, even when hospital acquired, may cause less morbidity and mortality than those due to pathogens such as MRSA or gram-negative bacteria that define much of the difference between community- and hospital-acquired infections.[106] Other recognized causes of community-acquired pneumonia are less often associated with pleural effusion and empyema, and the literature is dominated by pediatric cases. If a serologic diagnosis is accepted for disease caused by *Chlamydia pneumoniae,* 18 of 34 patients in a radiographic survey from Japan had mixed infections; of 24 of 30 who underwent CT scanning, 25% had parapneumonic effusion, similar to the rate found in the same population with *Mycoplasma pneumoniae* or *S. pneumoniae* pneumonia.[107] Molecular diagnosis of *M. pneumoniae* infection, problematic in the respiratory tract, might be more accurate in pleural fluid. The parapneumonic effusion associated with *M. pneumoniae* is usually lymphocyte predominant, and disease with effusion tends to occur in younger patients and lead to longer hospital stays.[108] *Haemophilus influenzae* in adults most often causes lower respiratory tract infections in patients with chronic obstructive pulmonary disease. The frequency of parapneumonic effusion in a recent report from Greece was 22%. Outcomes were strongly linked to the underlying disease.[109] Effusion occurred in 8 of 109 patients reported from Japan with *Moraxella catarrhalis* pneumonia. Emphysema was present in 67.9% and malignancy in 37.6%, which raises the issue of confounding diagnosis in the etiology of effusions.[110]

Legionella pneumophila and other *Legionella* species, *Legionella micdadei* prominent among them, may be associated with parapneumonic effusion. In a report of 61 nosocomially acquired cases of legionnaires' disease, effusions were present in the majority and were bilateral in 19%.[111] Hemorrhagic mononuclear cell–predominant effusion can occur as reported with *L. micdadei,* the Pittsburgh agent.[112]

The dominance of gram-negative empyema in reports from East Asia is remarkable. Although *K. pneumoniae* is the most frequent pathogen, it should be noted that diabetes mellitus is a major risk factor and the majority of isolates are not hyperviscous capsular types.[39,113]

Table 68.2 presents select infectious agents reported in empyema. Several categories emerge, including zoonotic pathogens (*Franciscella*

TABLE 68.2 Select Microorganisms Associated With Infected Pleural Effusion

PATHOGEN	ASSOCIATION	PLEURAL RATE	FLUID CHARACTERISTIC	RADIOLOGY	REFERENCE(S)
Extrapulmonary Disease					
Fusobacterium necrophorum, Prevotella spp.	Remote disease (septic thrombophlebitis)	15%–54%	31% empyema	Septic pulmonary emboli	248–250
Clostridioides difficile (formerly *Clostridium difficile*)	Remote disease (severe colitis)	35%–40%		In patients with abdominal CT, bilateral	251
Campylobacter jejuni	Dialysis	CR	Exudate, neutrophil predominant	Effusion without pneumonia	252
Campylobacter lari	Probable gastrointestinal source	CR	Empyema	Effusion without pneumonia	253
Salmonella enterica subsp. *enterica*	Contiguous	CR	Culture negative	Effusion without pneumonia	254, 255
Salmonella enterica subsp. *enterica*	Dissemination	CR	Empyema, peritonitis	NR	256
Salmonella enterica serovar *typhi*	Bacteremia	CR	Empyema	Bilateral effusion without pneumonia	257
Geographic/Environmental Association					
Burkholderia (Pseudomonas) pseudomallei	Coastal Asia, northern Australia Farming Diabetes mellitus	21%–36% PPE	Usually lymphocytic Transudate	PPE > effusion without pneumonia	258–260
Leptospira spp.	Water exposure	12.5%	Bloody fluid	Diffuse alveolar hemorrhage	261
Orientia tsutsugamushi	Coastal Asia, farmers	Pneumonia 21.6%, rare effusion	NR	Bronchopneumonia	262
Paragonimus kellicotti	Eating raw crayfish Eosinophils	In blood and pleural fluid in lung		Fever ± nodule in lung	263
Rickettsia rickettsii	Tick exposure	23% pulmonary manifestation 7% effusion	NR	Interstitial and alveolar infiltrates	264
Zoonoses					
Brucella spp.	Endemic zoonosis	10.8%–30.8% with effusion	Exudate by protein, culture positive, lymphocyte and mononuclear cell predominant	Interstitial > lobar pneumonia	265, 266
Coxiella burnetii	None reported	CR	Transudate, eosinophil predominant	Upper/middle lobe pneumonia	267
Chlamydia psittaci	Birds (pigeon breeder)	CR	Lymphocytic exudate, high ADA	PPE, consolidation	268
Francisella tularensis subsp. *tularensis*	Rabbits, cats	30%	Lymphocytic exudate, empyema, high ADA	Interstitial and lobar opacities, cavity rarer	269–271
Bartonella spp.	Zoonosis	CR	Exudate, lymphocyte predominant	Effusion without pneumonia	272
Immunocompromised State					
Rhodococcus equi	HIV infection Animal exposure not required	7.7% effusion	Frequent empyema	Upper lobe pneumonia, cavitation	273
Nocardia spp.	AIDS, renal transplant	10%–33%	Empyema in two-thirds	Cavitary pneumonia, upper to lower lobe 55%/35%	274–276
Campylobacter fetus	Immunoglobulin deficiency	CR	Exudate, lymphocyte predominant	Effusion without pneumonia	277
Cancer and Systemic Debility (Cardiac, Hepatic, and Renal Disease), Including Aspiration Risk					
Eikenella corrodens	CHF	31.5% with pleuropulmonary CA	Polymicrobial empyema	Pneumonia ± cavity	278
Listeria monocytogenes	CA; immunosuppressives	88.9% with CA	Mononuclear-predominant exudate	Effusion without pneumonia	279
Mycoplasma salivarium	CA	CR	Empyema	PPE	280
Actinomyces spp.	CA, hematologic malignancy	CR	Lymphocyte-predominant (ALL) empyema	Nodules, contiguous effusion	281

TABLE 68.2 Select Microorganisms Associated With Infected Pleural Effusion—cont'd

PATHOGEN	ASSOCIATION	PLEURAL RATE	FLUID CHARACTERISTIC	RADIOLOGY	REFERENCE(S)
Proteus mirabilis	CA, CHF	CRs	High pH (7.8–8.1) polymicrobial empyema	Effusions without pneumonia	282
Lactobacillus rhamnosus	COPD	CR	Empyema	Lung abscess	283
Campylobacter curvus	Bronchiectasis	CR	Empyema, polymicrobial	Upper lobe cavitation	284
Pasteurella multocida	Elderly, comorbidities	CRs, 62% with tube, 45% mortality	87% empyema	CPE	285
Campylobacter fetus subsp. *fetus*	Aspiration	CR	Empyema, mononuclear predominant	Contiguous abscess	286
Francisella tularensis subsp. *holarctica*	Immunocompromised	CR	Exudate, lymphocyte predominant	PPE, lobar infiltrate	287
Tropheryma whipplei	Unknown	CR, effusion in all 4 patients	NR	PPE	288
Lactococcus lactis subsp. *cremoris*	Aspiration, dairy products	CR	Empyema	Necrotizing pneumonia	289
Burkholderia (Pseudomonas) cepacia	Cancer, colonization	36%	NR	Cavitary pneumonia, PPE	290
Stenotrophomonas maltophilia	Health care acquired, immunocompromised	65% postsurgery, 30% fistula	Empyema, 77.5% polymicrobial	5% PPE	291
Clostridium perfringens	Cirrhosis	CR	Exudate, neutrophil predominant	Effusion without pneumonia	292
Bacillus cereus/ Clostridium bifermentans	Alcoholism	CR	Empyema	Necrotizing pneumonia	293
Mycoplasma hominis/ Ureaplasma urealyticum	Postsurgical mediastinitis, possible primary genitourinary source	CR	NR	Mediastinitis and pericarditis	294
Bioterrorism					
Bacillus anthracis	Inhalation	81.8%	NR	72.7% with infiltrates but with mediastinal widening	295

ADA, Adenosine deaminase; *AIDS,* acquired immunodeficiency syndrome; *ALL,* acute lymphoblastic leukemia; *CA,* cancer; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CPE,* complicated parapneumonic effusion; *CR,* case report; *CT,* computed tomography; *HIV,* human immunodeficiency virus; *NR,* not reported; *PPE,* parapneumonic effusion.

spp.), organisms with restricted or dominant geographic distribution (*Burkholderia pseudomallei*), infections predominantly associated with immunocompromising conditions (*Listeria, Nocardia* spp.), and pathogens that incidentally involve the pleural space during dissemination or involvement of contiguous structures. The data in case reports are often compromised by the interest of the author. For instance, radiographic literature often omits fluid analysis and other clinical information.

Viruses

An important consideration in viral disease and pleural effusion is the relatively recent development of rapid and sensitive molecular assays for diagnosis. In a study from 2013 in children with community-acquired pneumonia and effusion, 50% of cases had a viral diagnosis, and combined viral-bacterial infections were present in an additional 22%. Rhinovirus, enterovirus, influenza virus, respiratory syncytial virus, parainfluenza virus type 1, and several mixed infections were found.[114] Viral respiratory pathogens may be associated with effusion in lower respiratory tract disease. Adenovirus with effusion occurs in longer febrile illnesses, in which clinical management may be complicated and immunosuppressive conditions may be present at baseline.[115] Influenza in the 2009–2010 A(H1N1) epidemic was associated with effusions in all hospitalized cases in a radiology review, and respiratory failure was more likely in cases with radiographic evidence of pneumonia.[116] This was again demonstrated by CT scanning, but predominantly in immunocompromised hosts.[117] New types of influenza virus that have not so far demonstrated epidemic capacity and are associated with exposure to infected poultry, such as influenza A(H7N9), were associated with effusions in three of six cases, of which four died of adult respiratory distress syndrome.[118]

The resurgence of measles internationally necessitates mention of this preventable disease, which can cause respiratory distress associated with pleural effusion.[119] Viruses associated with capillary leak and pulmonary hemorrhagic syndromes have associated effusions, which may be bloody. Dengue virus is prominent among these, and a retrospective analysis of 363 dengue hemorrhagic fever patients found that 57.4% of abnormal chest x-rays had pleural effusions. The effusions sampled were transudative, suggesting a role for the vascular permeability problem common in this disease. Lassa fever, hantavirus pulmonary syndrome, and Crimean-Congo hemorrhagic fever are also reported.[120–123]

Herpesviruses, uncommon pulmonary pathogens, occasionally have manifestations that lead to effusion. Varicella-zoster virus has been detected in the pleural fluid of a patient receiving chemo- and radiotherapy for lymphoma.[124] Epstein-Barr virus, with an increasing spectrum of disease beyond infectious mononucleosis, was identified in the pleural fluid of 20 cases, all lung transplants. Viral burdens in pleural fluid were low but there was polymorphous lymphocytosis in >70% of cases.[125] Finally, Kaposi sarcoma–associated herpesvirus causes Kaposi sarcoma, primary effusion, or body cavity lymphoma. Virus is present in the effusion, though diagnosis of lymphoma is by cytology or flow cytometry.[126]

Newly identified syndromes with some geographic restriction may present with effusion, as reported in the severe acute respiratory syndrome coronavirus epidemic from 2004 in which 15% of patients had effusion at the initial presentation. The Middle East respiratory syndrome coronavirus, reported in 2015, was associated with effusion in 33% of patients in a small series, and there was increased mortality in the group with effusion.[127]

Finally, although the physiology is not obvious, hepatitis viruses may be associated with effusion. Hepatitis A infection may produce a sympathetic effusion from hepatic inflammation.[128] Hepatitis B has been associated with pleural effusion principally in case reports, for instance, when the effusion appeared in the context of exacerbations of chronic infection and without concomitant ascites.[129]

Mycobacteria Other Than Tuberculosis

Nontuberculous mycobacteria are sometimes associated with pleural disease. Nevertheless, the more frequent occurrence of pleural effusion with tuberculosis is a dominant differentiating feature in most reports that include disease caused by *Mycobacterium kansasii* or *Mycobacterium avium* complex (MAC).[130] In a report of nontuberculous mycobacteria pleurisy from Taiwan in the years 2000–2007, MAC most commonly showed more extrapleural involvement and occurred in patients with immune dysfunction. Of 19 cases, 9 were MAC, 5 rapidly growing mycobacteria, and 5 not otherwise characterized.[131] A new species, *Mycobacterium lentiflavum,* has been reported from Zambia, and in a second case report there was acute necrotizing pneumonia and parapneumonic effusion.[132,133] *Mycobacterium abscessus*, *Mycobacterium ulcerans* (after contiguous chest wall disease), and *Mycobacterium bovis* all appear in case reports with pleural effusion.[134–136]

Fungi

Fungal empyema may occur as a parapneumonic process, but increasingly is a complication of medical procedures and immunocompromising conditions. In an analysis from Taiwan from 1990 to 1997, 67 patients with fungal pleural infection were identified. An underlying condition was present in 85% and *Torulopsis glabrata* (now *Candida glabrata*) accounted for 60 of 73 isolates. The most common predisposition was abdominal disease or perforation. Patients who underwent surgery and pleural irrigation (11) survived, but the crude mortality was 73%. Determining attributable mortality is often not possible in such cases.[137] *Candida* spp. continue to be major pathogens in the context of gut disruption, with 55.6% of 63 cases of *Candida* empyema being associated with a gastrointestinal source and perforation.[138] Even with drainage, the mortality was high (62.5%) in a small series, revealing the association of this complication with high-morbidity/mortality predisposing conditions. *Candida* was responsible for 44% of pleural space infections in a series of consecutive lung transplant recipients whose pleural fluid was sampled in the 90 days after transplantation.[30]

Cryptococcus spp. are predominantly central nervous system and pulmonary pathogens in identified or uncharacterized immunodeficiencies but can involve the pleura in dissemination.[139] Pleural involvement is seldom a critical manifestation of disease, even in HIV infection.[140]

In HIV infection, *Pneumocystis jirovecii* is a major pulmonary pathogen but is rarely associated with pleural effusion.[141] *Pneumocystis* pneumonia with associated bilateral pleural effusions has been reported after hematopoietic stem cell transplantation.[142]

A newly identified dimorphic yeast-like fungus which forms hyphae in tissue, *Tilletiopsis minor,* has been found in the parapneumonic effusion of a child whose presentation suggests an undiagnosed immunodeficiency. Voriconazole may have been effective therapy when amphotericin B failed.[143]

Invasive molds involve the pleura by extension from infected lung. Pleural effusion is one of many factors that influences the outcome of invasive aspergillosis.[144] Late invasive aspergillosis occurred in 27 hematopoietic stem cell transplantation patients, with chronic corticosteroid use or graft-versus-host disease as the predisposing factor in 24, and effusions were present in 7.[145] The agents of mucormycosis have a characteristic pathology in pulmonary cases and in those that are associated with pleural effusion. Hemorrhage, gangrene, necrosis, infarction, and arterial thrombosis were present in 32 cases of invasive mucormycosis, of which 6 had unilateral and 3 bilateral pleural effusions.[146] The microbiologic differential of invasive molds in cancer patients may be influenced by an increased prevalence of pleural fluid in mucormycosis compared to aspergillosis (63% vs. 33%).[147]

Endemic or dimorphic mycoses may cause parapneumonic or isolated pleural effusions. *Histoplasma capsulatum* most commonly causes a self-limited illness that does not require therapy. Extensive disease, rupture of a juxtapleural cavity, or fibrosis may occur and be associated with pleural involvement.[148,149]

Coccidioides spp. are also associated with a self-limited acute illness, but pleural manifestations in disseminated disease follow the same risk factors as for dissemination in general. A pediatric series of 33 cases, however, noted effusions in 13, of which 4 were empyema.[150] The surgical pathology of pleural disease suggests that ruptured juxtapleural cavities are a major factor in cases in which spherules may be seen in biopsy or autopsy material from the pleural cavity.[151]

Blastomyces dermatitidis, in a large military survey from 1964, remains an uncommon pulmonary pathogen, and pleural manifestations are rare.[152] However, when pulmonary disease is present, a radiologic report of 63 cases found effusion in 13.[153]

Sporothrix schenckii rarely is a pulmonary or disseminated pathogen. A case report of a parapneumonic effusion found pleural fluid parameters consistent with an empyema (predominantly neutrophilic fluid with positive culture). The authors noted that this finding contradicted their presumption that such an effusion would be lymphocyte predominant.[154]

The literature on *Paracoccidioides brasiliensis* is sparse. A pathology series from Venezuela analyzed 11 autopsy and 20 surgical specimens and noted pleural involvement in 8, all with pulmonary disease.[155]

Talaromyces (previously *Penicillium*) *marneffei* is a cause of disseminated disease, mainly in HIV infected persons, in Southeast Asia. Disease diagnosed by pleural biopsy or pleural fluid analysis is reported.[156]

Parasites

Trichomonas spp. (usually *Trichomonas tenax*), which are flagylated protozoan parasites, are commensals of the oral cavity and thus are involved in pneumonias and associated effusion in the context of aspiration.[157]

Nematodes

Roundworms may infect the pleural space, either incidentally (*Toxocara canis, Gnathostoma* spp., and *Anisakis simplex*) or in relationship to their role as intrathoracic pathogens *(Dirofilaria immitis)*.[158–161] *Strongyloides stercoralis* may involve the pleural space during dissemination.[162]

Filarial pathogens *(Loa loa, Wuchereria bancrofti)* appear in case reports with pleural involvement, the former with and the latter without eosinophilic fluid.[163,164]

Cestodes

Echinococcus spp. tapeworms cause pulmonary hydatid cyst, and the pleura can be involved by rupture of a lung cyst, but the more common complication is transdiaphragmatic involvement from a ruptured liver cyst. Uncomplicated effusion (sometimes eosinophilic) or empyema can occur in 1% to 16% of cases of hepatic hydatid disease.[165,166]

Trematodes

The lung fluke (*Paragonimus* spp.) causes pleural complications as a natural component both of its role as a pulmonary pathogen and the presumed route of pulmonary infection, which may involve migration out of the gastrointestinal tract through the diaphragm. Disease may be mistaken for pulmonary tuberculosis. Subpleural or subfissural parenchymal disease is present in 87% of cases.[167,168] Effusion, sometimes eosinophilic and occasionally massive and persistent, appears in many reports. Worms may be found in the pleural fluid.[169] Pulmonary and pleural disease from *Paragonimus kellicotti,* usually associated with ingestion of inadequately cooked crayfish in North America, had an eosinophilic pleural effusion as a major manifestation in a series of eight patients from a single institution. CT may demonstrate a track connecting the pleura to the parenchyma.[170,171]

Other Parasites

In a report from California, hepatic amebiasis was complicated by pleural effusion in 9 of 30 patients, of whom 60% were symptomatic. Effusions, when sampled, were exudative, with high protein and LDH ratios and neutrophil predominance, but no parasites were detected.[172]

Parasitic infections may disseminate and involve the pleural space in HIV infection. Microsporidia (*Enterocytozoon bieneusi*), *Trypanosoma cruzi* (Chagas disease), and *Leishmania donovani* have been found in

TABLE 68.3 Evolution of Studies Defining Pleural Fluid Characteristics and Diagnoses

AUTHOR, REFERENCE	POPULATION	TEST/FINDING/INTERPRETATION
Paddock[296]	Defined cardiac, neoplastic, tuberculous, and infected effusions	Specific gravity as a test performs poorly in cardiac and nontuberculous infected effusions, neoplastic effusions both transudative and exudative.
Carr and Power[297]	Defined cardiac, neoplastic, and tuberculous effusions	Testing protein, a concentration greater than 3 g/dL was present in 92.8% of neoplastic and all tuberculous effusions but cardiac effusions perform variably.
Chandrasekhar et al.[298]	Defined malignant, pyogenic (tuberculosis and other), and transudative effusions	Testing lactate dehydrogenase (LDH) and protein, all transudative effusions were cardiac and hepatic, LDH cutoff an arbitrary 550 IU/mL; 22/24 cancer and all infectious effusions identified, but protein performed poorly in transudates.
Light et al.[185]	Defined cancer, heart failure, tuberculosis, and others (parapneumonic)	Protein alone poor (19% error with malignancy). Effusion to serum protein <0.5 accurate for transudates. LDH <200 IU/L accurate for transudates, effusion to serum LDH >0.6 IU/L more accurate for exudates. Combine LDH, protein, and LDH ratios for best accuracy.
Light et al.[188]	Infected effusions	To predict which parapneumonic effusions will become empyemas, low pH (cutoff 7.20) separated intervention-requiring disease better than cell count and protein.
Potts et al.[299]	Infected effusions	pH was the only nonoverlapping factor, more predictive than negative Gram stain or negative culture.
Light et al.[183]	Admitted pneumonias screened for parapneumonic effusion and progression to complicated effusion/empyema	Incidence of parapneumonic effusion 44.4%, 10/37 sampled were complicated (5% of the population). All pH <7.0 and glucose <40 mg/dL were complicated, all pH >7.2 or LDH <1000 IU/L were uncomplicated.
Sahn and Light[300]	Editorial on defining the need for intervention, relevant only to parapneumonic effusions	Summary standards: uncomplicated effusion pH >7.30, glucose >60 mg/dL, pleural fluid-to-serum protein ratio >0.5, LDH <1000 IU/L. Complicated effusion (with empyema) pH <7.10, glucose <40 mg/dL, LDH >1000 IU/L. Drainage for positive Gram stain, pH <7.10, glucose <40 mg/dL.
Valdes et al.[301]	Defined effusions in cardiac, cancer, tuberculosis, and miscellaneous/ infected (parapneumonic) disease	All transudates had pleural cholesterol <55 mg/dL, but this misclassified 11.9% of cancer cases, 6% of tuberculosis cases, and 8.9% of miscellaneous cases (exudates called transudates). Superior to LDH and LDH ratio but not significantly different than Light (4). Strong positive predictive value, negative predictive value only 79%.
Burgess et al.[302]	Defined population, reconciling acknowledged misclassification of some transudates as exudates after therapy (diuresis) or chronic	In patients in whom a transudative process (heart failure, cirrhosis, or renal failure) is miscategorized by Light criteria as an exudate, the serum-to-effusion albumin gradient (serum albumin minus effusion albumin <1.2 g/L) may reconcile misclassification (especially with diuretics), but overall is less accurate than Light criteria.
Vives et al.[303]	Record review to classify transudates and exudates in defined population	Attempts to improve misclassification by raising the protein ratio, LDH ratio, or absolute LDH value provided little benefit.

pleural fluid in this context.[173–175] Rarely, in HIV-infected or non–HIV-infected persons, *Leishmania chagasi,* an agent of visceral leishmaniasis, may be found in effusions and mimic tuberculosis.[176,177]

Infestation by the causative agent of cutaneous myiasis was associated with recurrent migratory subcutaneous nodules and an eosinophilic pleural effusion.[178]

DIAGNOSIS

Diagnostic tests identify causes but also stratify risk and direct interventions to prevent adverse outcomes. A parapneumonic effusion should be sought in cases of pneumonia, since 40% or more of patients have pleural fluid and the presence of effusion is associated with adverse outcomes, the risk of which is amplified by inadequate evaluation.[179] Physical findings may decrease the likelihood of pleural fluid (normal chest expansion, no dullness to percussion), but positive findings (vocal fremitus, percussion and breath sound changes) are insufficiently specific.[180]

Obtaining bilateral decubitus films or performing more sensitive tests such as CT scans may reveal effusions not visible on posterior-anterior or lateral views. Lower lobe pneumonias may cause standard films to miss 10% of effusions.[181] CT and ultrasound both have roles in identification of effusions, but importantly, neither has the ability to adequately characterize the fluid.[182] Fluid analysis is required. Radiographic indications for fluid sampling might include fluid thickness >1 cm on routine chest x-ray or >2 cm on CT.[183] Ultrasound improves the accuracy of fluid sampling, even by experienced physicians, and can identify septations/loculations that may be missed by CT scan.[184]

As discussed elsewhere, fluid characteristics (transudate, exudate, empyema) direct therapies and interventions. Small transudative effusions may require no further sampling or drainage, especially if the course of treatment for the primary cause (pneumonia, for instance) is satisfactory. Exudative effusions in an early phase, without loculation, may respond to closed thoracostomy (chest tube drainage). Empyemas routinely require drainage and, because they are often loculated, early aggressive therapy may be necessary to avoid adverse outcomes and more aggressive surgical techniques such as open thoracotomy.

Fluid Analysis

The evaluation of pleural fluid should include simultaneous measurements of serum and pleural fluid LDH, albumin, protein, and glucose. Specimens should be stained and cultured for bacteria, fungi, and mycobacteria. Molecular assays and other surrogates are used in the appropriate context. The classic criteria identified by Light and colleagues in 1972 continue to perform with high sensitivity and specificity, but have been modified, particularly for the evaluation of parapneumonic effusions.[183,185] The historical sequence of testing is presented in Table 68.3 to illustrate a very important point. The clinical scenario has always defined the likely character of an effusion. Studies have been performed, as noted in the table, in a "defined" population (known cancer, heart failure, tuberculosis, etc.) with an effusion characteristic of the disease (transudate in CHF, exudate in tuberculosis) to determine the degree to which any test is consistent with clinical judgment. Thus a change in fluid parameters outside of the presumed range for a clinical condition means that causes for the change must be sought. It should be noted that these studies do not conform to a contemporary standard by which a population would be studied, parameters established, and then a second population used to validate the results (see the earlier discussion of the risk score derived from the MIST studies).

Failure of Light's criteria was recognized early and is usually related to misclassification of fluid that should be associated with a noninfectious process (CHF) as an exudate. Diuresis may promote this problem. In the context of low clinical suspicion for infection and the presence of CHF, the addition of serum-to-effusion protein and albumin gradients can be informative.[186] Multiple additional parameters have been suggested, but no addition to Light's criteria, with the possible exception of the serum-to-effusion cholesterol ratio, either is practical or performs well.[187]

The addition of pleural fluid pH is an important parameter in parapneumonic effusions.[188] Very low pH outweighs many other parameters in predicting the need for aggressive management.[183] Determination of pH should be performed on a blood gas analyzer immediately after the pleural fluid is drawn, and residual air and lidocaine or heparin should be minimized because they alter results.[189] Physicians routinely are unaware of the technology used in their institutions for pH measurement, and results are compromised by this lack of knowledge.[190]

Three automated systems utilizing inoculation of pleural fluid into liquid media are available (Biomerieux BacT/Alert, Becton Dickinson BACTEC MGIT [for mycobacteria], and Thermo Scientific VersaTrek). These may hasten results and improve the sensitivity of culture.[191–193] Inoculation of solid media may be necessary to isolate mixed flora, such as obligate anaerobes mixed with more rapidly growing facultative anaerobes. Fluid samples should be obtained directly from the effusion, not drawn from chest tubes or other drainage devices. Additional specific microbiologic diagnostics were discussed earlier in the chapter.

Pleural biopsy was established in the 1950s as a high-yield procedure, especially for the diagnosis of tuberculous pleurisy, because the additional histopathologic evidence and culture of tissue increase the sensitivity of microbiologic diagnosis substantially.[194,195]

TREATMENT

Because of the variety of infectious agents and the changing patterns of drug susceptibilities and available antimicrobials, drug therapy can only be addressed in broad terms.

Two general trends in the treatment of bacterial empyema have emerged. First, gram-negative organisms and MRSA are important, especially in the same settings in which they are responsible for hospital-acquired pneumonia, so those organisms' drug susceptibility should be taken into account early.[96,113,196] Second, in adults with a predisposition to aspiration or obstructive disease from cancer that leads to effusion and empyema, limiting the spectrum of treatment to a noncarbapenem β-lactam without a β-lactamase inhibitor or a cephalosporin without metronidazole is inappropriate.[102,103] Other considerations should be made as discussed in organism-specific chapters of this text.

Data on the specifics of antibiotic activity and pharmacokinetics in the pleural space are limited. Aminoglycosides should not be used to treat empyema.[197] Daptomycin's protein binding, purportedly the cause of its limited role in pulmonary infection in general, might play a negative role in exudative effusions. A wide spectrum of drugs, many no longer commonly used, have been studied.[83] Quinolones have been found to have variable penetrance into pleural effusions, but the clinical consequences of the reported levels remain unclear.[198] Clarithromycin, azithromycin, linezolid, and ertapenem have been studied in experimental settings and levels achieved are consistent with inhibition of growth of organisms normally targeted by these agents.[199–201]

Although repeat thoracentesis has been practiced, it is no longer recommended, and empyema should be treated with more aggressive drainage measures. Small-bore catheters have proven effective in tube thoracostomy, and flushing of catheters (e.g., with 20 mL of saline every 6 hours) may facilitate continued patency of the tube.[202,203] Additional measures have been studied in an attempt to avoid surgery. The physiology of complicated effusion and empyema was demonstrated early, with streptococcal fibrinolysin (streptokinase) and deoxyribonuclease (DNase) improving drainage and outcomes in a study in 1949.[204] DNase predominantly decreases pus viscosity.[205] The role of fibrinolytics in breaking down loculations to improve chest tube drainage has been reported in multiple studies. Notably, MIST 1 found no effect on mortality, rate of surgery, or length of stay, but was criticized on the grounds of enrollment criteria, radiographic evaluation and stratification, and some management decisions.[206] MIST 2 used the same definition of loculation (chest x-ray presence of pleural fluid or thickening not distributed in accordance with gravity), with a different fibrinolytic (recombinant tissue plasminogen activator) and recombinant DNase. The goal was to decrease the area of pleural opacity; 210 subjects were enrolled, and combination therapy was significantly effective compared to placebo. Significant secondary effects of reduced surgical referral and length of stay, but not reduced mortality, were found.[207] Nevertheless, the heterogeneity of patients, perhaps as defined in the criticism of MIST 1, have led both the BTS and the AATS to consider the results inconclusive and recommend against the routine use of fibrinolytics.[7,8]

The transition to more aggressive measures depends on the severity, extent, and chronicity of disease. Video-assisted thoracoscopic surgery (VATS) is a procedure that requires surgical anesthesia, double-lumen intubation, and deflation of the affected lung. In patients unable to tolerate this, medical thoracoscopy, although less studied as an intervention, seems to achieve acceptable rates of success with conscious sedation and without the use of an operating room. When expertise in the procedure is available, VATS, medical thoracoscopy, or open surgery are procedures whose aim is to achieve full evacuation of infected fluid and decompression of the affected lung.[208]

Although much studied in pediatrics, indications for VATS in adults are more poorly defined.[209,210] Medical failure must be defined and the morbidity and cost of VATS as an intermediate-stage intervention before thoracotomy must be considered. A randomized trial enrolling 20 patients in 1997 compared tube thoracostomy with fibrinolytics versus VATS for loculated, complex fibrinopurulent parapneumonic empyema. VATS showed a higher success rate, but VATS was also successful in rescuing failed chest tube/fibrinolytic therapy, clouding the issue of whether VATS was necessarily the first-line therapy.[211]

A prospective trial of 179 adults with empyema established that 42% ultimately needed decortication, with progression to decortication in 24 (decortication was the primary therapy in 52), but this was in a setting in which VATS was not offered. Without decortication, nevertheless, 103 patients (58%) were cured.[47] Delaying VATS reduces its success rate because visceral pleural thickening progresses and impedes lung reexpansion. At this stage, empyema is longer amenable to VATS even when microbiologic treatment has been successful (Fig. 68.3). When VATS is used earlier, there is faster postoperative recovery than with thoracotomy.[212]

An important retrospective review of 104 cases from 2000 to 2006 is illustrative of the general tendency in the literature and its shortcomings. This study stratified patients according to American Thoracic Society criteria, but further stratified stage II disease into types A and B based on the presence of a pleural peel in the latter. The choice of simple drainage (pigtail catheter or chest tube) was the strongest predictor of death or need for further procedure, but was still adequate/definitive treatment in 60 patients with stage I empyema, and the study did not attempt to address better staging. In addition, there was no control for conditions that determined VATS versus thoracotomy, thus the resultant inability to determine that the division in stage II (A/B) made a difference.[213] Additional confounding factors are present in a population-based analysis of 4424 patients hospitalized with pleural infection. In addition to showing increased rates of disease during the period studied and significant imbalances related to younger age and lower comorbidity in patients undergoing surgery, adjustment for those factors still yielded a 58% lower risk of death in those undergoing operative therapy.[214]

Options related to the management of stage III empyema are related to the achievement of adequate evacuation of infected space and reexpansion of affected lung. The organization present in chronic empyema requires VATS or thoracotomy. There is no evidence to support antibiotic instillation into an infected space, although this was the basis of the Clagett procedure, in which a hole in the chest wall was created for periodic antibiotic instillation.[8,215,216]

A problem can arise when the lung cannot expand to fill empyema space in the thoracic cavity because of lung resection or pleural fibrosis. When infection cannot be controlled, closing the space could be beneficial. Resection of the anterior ends of the lower ribs, called *thoracoplasty,* was designed to bring the chest wall toward the remaining lung. A persistent bronchopleural fistula was a relative contraindication for thoracoplasty and needed surgical repair. An even more intractable empyema can occur in a postpneumonectomy thoracic cavity. When empyema treatment fails and long-term chest tube drainage is used, an alternative is formation of an opening through the skin into the base of the thoracic cavity, allowing spontaneous drainage. Although rarely used now, this approach is termed an *Eloesser flap.*[217] Fortunately, improvements in antimicrobial therapy and early, effective treatment of empyema have made these procedures rare.

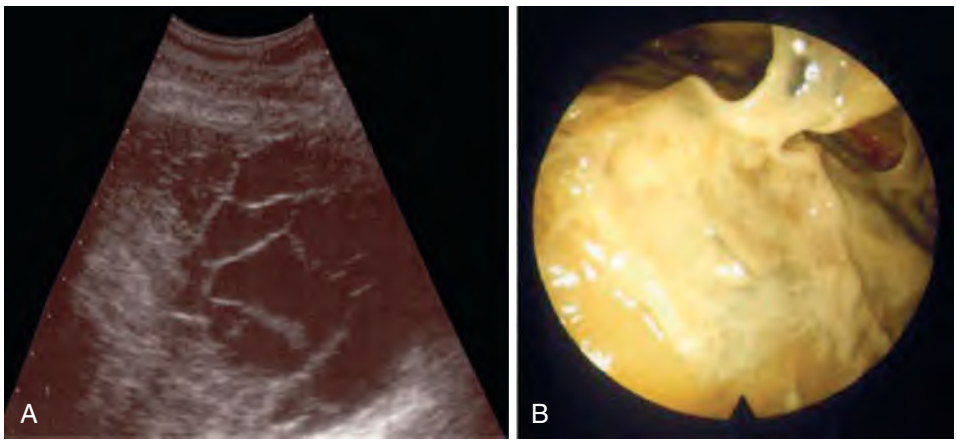

FIG. 68.3 Multiloculated pleural empyema. (A) Ultrasonographic image of a multiloculated pleural empyema and (B) extensive fibrin deposition with septation and pockets of pus as seen during a medical thoracoscopy in a patient with multiloculated pleural empyema (category 7 according to Light[11]). Such septae prevent a successful evacuation of pus by simple chest tube drainage. *(From Brutsche MH, Tassi GF, Gyorik S, et al. Treatment of sonographically stratified multiloculated thoracic empyema by medical thoracoscopy.* Chest. *2005;128:3303–3309.)*

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69 Bacterial Lung Abscess

Joanna K. Nelson and Julie Parsonnet

SHORT VIEW SUMMARY

Definition
- Lung abscess is defined as localized necrosis of infected lung tissue resulting in one or more cavities.

Epidemiology
- Primary lung abscess occurs in the setting of aspiration, usually with altered consciousness and gingival disease.
- Secondary lung abscess occurs as a result of airway obstruction or immunosuppression.

Microbiology
- Lung abscesses are polymicrobial, typically involving oral microbiota including streptococci and anaerobes.

Diagnosis
- Chest imaging shows a thick-walled cavity with an air-fluid level in the appropriate clinical setting.

Therapy
- Treatment entails weeks of antibiotic therapy with a β-lactam/β-lactamase combination, clindamycin, or moxifloxacin.

Prevention
- Aspiration precautions and maintenance of oral hygiene can be helpful in preventing aspiration pneumonia and lung abscess.

DEFINITION

Lung abscess is a localized area of infected, necrotic lung tissue with one or more cavities. Lung abscess is part of a continuum of necrotic lung infections previously known as "lung gangrene."

Lung abscesses can be classified as primary or secondary. Primary lung abscesses, which comprise 80% of all lung abscesses, occur as a result of aspiration of oral or gastric contents into the lungs. In contrast, the inciting factor in secondary abscesses is underlying disease—for example, intrinsic (e.g., tumor or infectious mass) or extrinsic (foreign body) airway lesions, deficient host defense mechanisms, or thoracic surgery. Lung abscesses can also be divided into acute (symptoms for ≤4 weeks) or chronic (symptoms for >4 weeks). The term "putrid" lung abscess is used to describe those with foul-smelling sputum. Lung abscess can also be defined according to the causative organism.

PATHOPHYSIOLOGY

A delicate interplay among the host microbiome, potential pathogens, and local immunity in the lung is at work in a healthy respiratory system. Any disturbance of this homeostasis can result in lung pathology including pneumonia and lung abscess.[1] Within the microbiome of the respiratory tract as a whole, there are discrete anatomic microbiomes, each with its own subset of commensals. Next-generation sequencing of samples taken from the respiratory tract has shown variable combinations of bacteria, fungi, and viruses based on their anatomic location in the respiratory tree, likely resulting from local environmental factors (Fig. 69.1).[2] Despite the overall diversity of microbes found along the respiratory tract, the microbiome of the lung often reflects that of the upper respiratory tract, specifically the oropharynx.[3] Accordingly, colonization of the upper respiratory tract is often a prerequisite for a pathogen to later cause lower respiratory tract infection.[4] However, the lung does not merely represent the oropharynx; local environmental factors in the lung can result in selection of particular organisms, and nonoral microorganisms have established unique niches in the lung itself.[5]

Bacteria can enter the deeper lung airways by means of microaspiration from the upper respiratory tract.[6] Approximately half of healthy individuals demonstrate subclinical aspiration during sleep.[7,8] This aspiration is infrequently of clinical consequence, presumably owing to the low burden of virulent bacteria in aspirated material and to intact local immune defenses, including cough and ciliary transport, and humoral and cellular immune responses. Any condition that increases the bacterial inoculum of aspirated material or impairs host defense mechanisms, however, may lead to aspiration pneumonia and occasionally lung abscess.[9]

Most lung abscesses are polymicrobial infections involving organisms from the oropharynx.[10] In experimental animal models from early in the 20th century, bacteria isolated from lung abscesses at autopsy resembled those in the gingival crevice. Based on this finding, aspiration of oral flora was concluded to be the mechanism of infection.[11,12] Inoculation of animals with four anaerobic bacteria together, but not singly, reproduced the disease, supporting synergistic effects of the bacteria in inducing necrosis and abscess.[11,12]

Once oral contents have been aspirated, ensuing pathology varies from chemical pneumonitis to pneumonia, necrotizing pneumonia, and lung abscess.[11] Aspirated bacteria are carried by gravity to dependent portions of the lung. In a supine individual, the right main stem bronchus is larger and at less of an angle than the left; consequently, lung abscesses occur most frequently in the posterior segment of the right upper lobe. Chemical injury from aspirated gastric acid or obstruction from aspirated particulate matter further predisposes to infection. Resulting inflammation may also provide a favorable environment for certain pathogenic bacteria, particularly gammaproteobacteria, allowing these organisms to grow and outcompete other microbes on the mucosal surface. In a vicious cycle, these bacteria may then contribute to further inflammation and lung destruction.[3] Studies of animal models have shown that tissue necrosis with lung abscess formation takes at least 6 to 7 days.[11,12] In humans, sequential monitoring of chest radiographs after a known aspiration revealed that abscesses typically required at least 7 to 14 days to develop.[13]

Other processes that can lead to anaerobic lung infections include secondary infections of bland pulmonary infarct; postobstructive processes, from either neoplasm or foreign body; or bronchiectasis. The common theme is stasis or necrosis of tissue that presumably serves as a nidus for polymicrobial infection.[14] Pulmonary infarction due to embolism through the pulmonary artery usually does not lead to lung cavitation in the absence of either congestive heart failure or septic pulmonary emboli.

Although less common, monomicrobial abscesses occasionally do occur, usually in the setting of septic embolization from right-sided endocarditis or septic thrombophlebitis. Abscesses arising from a hematogenous source typically manifest as multiple peripheral lesions on chest images (Fig. 69.2).[15] Monomicrobial lung abscesses without