

GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Community-Acquired Pneumonia in Adults: Guidelines for Management

**John G. Bartlett, Robert F. Breiman, Lionel A. Mandell,
and Thomas M. File, Jr.**

From the Johns Hopkins University School of Medicine, Baltimore, Maryland; the Centers for Disease Control and Prevention, Atlanta, Georgia; McMaster University, Hamilton, Ontario, Canada; and the Northeastern Ohio Universities College of Medicine, Akron, Ohio

This is part of the series of practice guidelines commissioned by the Infectious Diseases Society of America through its Practice Guidelines Committee. The purpose of this guideline is to provide assistance to clinicians in the diagnosis and treatment of community-acquired pneumonia. The targeted providers are internists and family practitioners. The targeted groups are immunocompetent adult patients. Criteria are specified for determining whether the inpatient or outpatient setting is appropriate for treatment. Differences from other guidelines written on this topic include use of laboratory criteria for diagnosis and approach to antimicrobial therapy. Panel members and consultants are experts in adult infectious diseases. The guidelines are evidence based where possible. A standard ranking system is used for the strength of the recommendations and the quality of the evidence cited in the literature reviewed. The document has been subjected to external review by peer reviewers as well as by the Practice Guidelines Committee and was approved by the IDSA Council. An executive summary and tables highlight the major recommendations. The guidelines will be listed on the IDSA home page at <http://www.idsociety.org>.

—Peter A. Gross, MD, for the
IDSA Practice Guidelines Committee

Executive Summary

Lower respiratory tract infections are the major cause of death due to infectious diseases in the United States. Despite substantial progress in detection of pathogens and in therapeutic options, there continue to be major controversies in the clinical management of these infections. This document represents the guidelines of the Infectious Diseases Society of America. The guidelines are applicable only to immunocompetent adult patients with community-acquired pneumonia.

Diagnostic studies: The document provides recommendations for the evaluation of patients with suspected pneumonia, including the pivotal role of chest radiography to confirm the presence of a parenchymal infiltrate. Prognostic factors are defined, including indications for hospitalization. Many of the decisions to hospitalize patients are influenced by analyses from the Pneumonia Patient Outcomes Research Team, which have now been validated in clinical practice.

Recommended diagnostic studies include blood cultures and gram staining and cultures of expectorated sputum for patients who require hospitalization. Caveats in this recommendation address the need for pretreatment specimens that are expeditiously transported and undergo cytologic screening as contingencies for optimal results. Tests for the presence of *Legionella* species, preferably culture and urinary antigen assay, should be performed for a subset of patients. Other diagnostic tests for specific microbial pathogens are recommended, but these tests are not considered routine. Some organisms are considered diagnostic as the cause of pneumonia when detected in any specimen; most potential pathogens recovered from expectorated sputum represent possible contaminants from the upper airways; thus interpretation of their recovery is dependent on clinical correlations, gram stain findings, and quantification in cultures.

Selected topics are discussed individually as well as within the context of the broader perspective of all patients with pneumonia. These topics include pneumococcal pneumonia; aspiration pneumonia; pneumonia caused by anaerobic bacteria, *Chlamydia pneumoniae*, *Legionella* species, and *Mycoplasma pneumoniae*; Hantavirus pulmonary syndrome; *Pneumocystis carinii* pneumonia; influenza; and empyema.

Treatment: Therapeutic recommendations are provided in two categories. The first category includes the recommendations that apply when a pathogen is detected, i.e., pathogen-directed therapy based on in vitro susceptibility test results

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Reprints or correspondence: Dr. John G. Bartlett, Johns Hopkins Hospital, AIDS Clinical Trials Unit, Baltimore, Maryland 21205.

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and/or clinical trials. Penicillin or amoxicillin are recommended for strains of *Streptococcus pneumoniae* that show susceptibility or intermediate resistance (MIC, $\leq 1.0 \mu\text{g/mL}$). For strains with high-level resistance (MIC, $\geq 2 \mu\text{g/mL}$), the recommendation is based on results of in vitro testing; for empirical use, a fluoroquinolone with good antipneumococcal activity or vancomycin is recommended. Other microbe-specific recommendations are based on predicted in vitro activity and results of clinical trials or clinical experience.

The second category of treatment recommendations applies when no etiologic diagnosis has been made and decisions on empirical antibiotic therapy are required. For this group of patients, the guideline provides multiple options because of the lack of clinical trial data that clearly identify superior regimens and the desire to encourage use of a broad range of drugs. The recommendations for outpatients are a macrolide, a fluoroquinolone with good activity against *S. pneumoniae*, or doxycycline. The recommendation for hospitalized patients is a β -lactam (cefotaxime, ceftriaxone, or a β -lactam- β -lactamase inhibitor) with or without a macrolide; an equally acceptable option is a fluoroquinolone with good antipneumococcal activity and established efficacy for atypical pneumonia (pneumonia due to *Legionella* species, *C. pneumoniae*, or *M. pneumoniae*). For seriously ill patients, emphasis is placed on adequate coverage for *S. pneumoniae* and, less commonly, *Legionella* species as the major causes of lethal pneumonia. The recommendations for empirical therapy are for a β -lactam combined with erythromycin, azithromycin, or a fluoroquinolone. However, the Panel recognizes that local factors such as susceptibility patterns and epidemiologically important pathogens may dictate alternative options.

Therapy with parenteral agents usually may be changed to oral antimicrobial treatment, and patients can be discharged from the hospital when there is evidence of a clinical response and ability to tolerate oral medications. The recommended duration of treatment for pneumococcal pneumonia is 72 hours after the patient becomes afebrile. Most other forms of pneumonia caused by bacterial pathogens are treated for 1–2 weeks after patients become afebrile. Atypical pneumonia is usually treated for 10–21 days.

Response: Failure to respond is ascribed to multiple factors, but most commonly represents inadequate host defense; less

Table 1. Categories reflecting the strength of each recommendation.

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

NOTE. Data are from [1].

Table 2. Categories indicating the quality of evidence on which recommendations are made.

Grade	Definition
I	Evidence from at least one randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Data are from [1].

common causes include erroneous drug selection, dosage regimen, or diagnosis; an unusual pathogen; or dual infections or complications such as empyema. Diagnostic options in such cases include CT imaging, bronchoscopy, and diagnostic studies for alternative diagnoses.

Prevention: The recommendations also address the important role of prevention, with major emphasis on guidelines for proper use of influenza and *S. pneumoniae* vaccines.

Introduction

Lower respiratory tract infections are the major cause of death globally and the major cause of death due to infectious diseases in the United States. Recent advances in the field include the identification of new pathogens (*C. pneumoniae* and hantavirus), new methods of microbial detection (PCR), and new antimicrobial agents (macrolides, β -lactam agents, fluoroquinolones, carbapenems, and streptogramins). Despite extensive studies, there are few medical conditions that are so controversial in terms of management. Guidelines for management were published in 1993 by the American Thoracic Society (ATS) [1], the British Thoracic Society [2], and the Canadian Infectious Disease Society [3]. The present guidelines represent recommendations of the Infectious Diseases Society of America (IDSA). In contrast to prior guidelines, these are intended to reflect updated information, more-extensive recommendations in selected areas, and an evolution of opinion. These therapeutic guidelines are restricted to community-acquired pneumonia (CAP) in immunocompetent adults.

Recommendations are given alphabetical ranking to reflect their strength and a Roman numeral ranking to reflect the quality of supporting evidence (tables 1 and 2). This is customary for quality standards from the IDSA [4]. It should be acknowledged that no set of standards can be constructed to deal with the multitude of variables that influence decisions regarding site of care, diagnostic evaluation, and selection of antibiotics. Thus, these standards should not supplant good clinical judgment.

Epidemiology

Magnitude

CAP is commonly defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection and is accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales) and occurs in a patient who is not hospitalized or residing in a long-term-care facility for ≥ 14 days before the onset of symptoms. Several symptoms of acute lower respiratory tract infection (in most studies at least two) may be present, including fever or hypothermia, rigors, sweats, new cough with or without sputum production or change in the color of respiratory secretions in a patient with chronic cough, chest discomfort, or the onset of dyspnea. Most patients also have nonspecific symptoms such as fatigue, myalgias, abdominal pain, anorexia, and headache.

Pneumonia is the sixth most common cause of death in the United States. Between 1979 and 1994, the overall death rates associated with pneumonia and influenza increased by 59% (on the basis of discharge diagnostic codes) in the United States [5]. Much of this increase is attributable to a greater proportion of persons ≥ 65 years of age; however, age-adjusted rates also increased by 22%, suggesting that other factors may also have contributed to a change in the epidemiology of pneumonia. These factors include the fact that a greater proportion of the population has underlying medical conditions, placing such persons at increased risk of respiratory infection.

Annually, 2–3 million cases of CAP result in ~ 10 million physician visits, 500,000 hospitalizations, and 45,000 deaths in the United States [6, 7]. The incidence of CAP requiring hospitalization is estimated to be 258 cases per 100,000 population and 962 cases per 100,000 persons ≥ 65 years of age [7]. While mortality has ranged from 2% to 30% among hospitalized patients in a variety of studies, the average rate is $\sim 14\%$ [8]. Mortality is estimated to be $< 1\%$ for patients who are not hospitalized [8, 9]. The incidence of CAP is highest in the winter months.

Risk Factors for Mortality

Risk factors for a lethal outcome from pneumonia were well defined in the pre-penicillin era; studies in adults showed a direct correlation with age, the presence of leukocytosis, bacteremic vs. nonbacteremic cases, extent of quantitative bacteremia, extent of radiographic changes, and extent of alcohol consumption [10]. More-recent studies have continued to show that most of these clinical features, including age [11, 12] and alcoholism [2, 13] are risk factors; a contributing role for multiple associated conditions such as active malignancies [8, 9, 14, 15], immunosuppression [11, 14–16], neurological disease [8, 9, 16, 17], congestive heart failure [8, 16, 17], and

diabetes mellitus [12, 18] has also been shown. Previous pneumonia also appears to be a risk factor for death [19]. Clinical settings that are associated with higher mortality rates are the presence of infections due to gram-negative bacilli or *Staphylococcus aureus*, postobstructive pneumonia, or aspiration pneumonia [8, 14]. High alcohol intake has been associated with an increased incidence of pneumonia [10, 20].

Investigators from the Pneumonia Patient Outcomes Research Team (PORT) have developed a prediction rule that stratifies patients into five classes by using a cumulative point system based on 19 variables (figure 1) [9]. The rule was validated with retrospective analysis of 38,039 inpatients, which showed a direct correlation between class and mortality (table 3). On the basis of these observations, the authors concluded that their prediction rule identifies patients with CAP who are at risk for death and other adverse outcomes. The authors further suggest that the prognosis is sufficiently good in categories 1–3 to consider outpatient management, or outpatient management for categories 1 and 2 with a brief observational hospital stay for category 3; patients in categories 4 and 5 would undergo traditional hospitalization. The Panel endorses the findings of the PORT studies as valid predictors for mortality as well as the use of these observations as a rational foundation for decisions regarding hospitalization. Nevertheless, there are multiple other factors to consider in the decision about site of care, including compliance and quality of home support [21]. It should be emphasized that the observations in the PORT study were validated as predictors of mortality and not as a method for triaging patients; the authors also emphasize that the prognostic score should not supercede clinical judgement in the decision to hospitalize [8, 21].

Role of Specific Pathogens in CAP

Prospective studies for evaluating the causes of CAP in adults have failed to identify the cause of 40%–60% of cases of CAP, and two or more etiologies have been identified in 2%–5% of cases [2, 7, 22–25]. The most common etiologic agent identified in virtually all studies of CAP is *Streptococcus pneumoniae*, and this agent accounts for approximately two-thirds of all cases of bacteremic pneumonia [8]. Other pathogens implicated less frequently include *Haemophilus influenzae* (most isolates of which are other than type B), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *S. aureus*, *Streptococcus pyogenes*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and other gram-negative rods, *Legionella* species, influenza virus (depending on the time of year), respiratory syncytial virus, adenovirus, parainfluenza virus, and other microbes. The frequency of other etiologies, e.g., *Chlamydia psittaci* (psittacosis), *Coxiella burnettii* (Q fever), *Francisella tularensis* (tularemia), and endemic fungi (histoplasmosis, blastomycosis, and coccidioidomycosis), is dependent on specific local epidemiological factors.

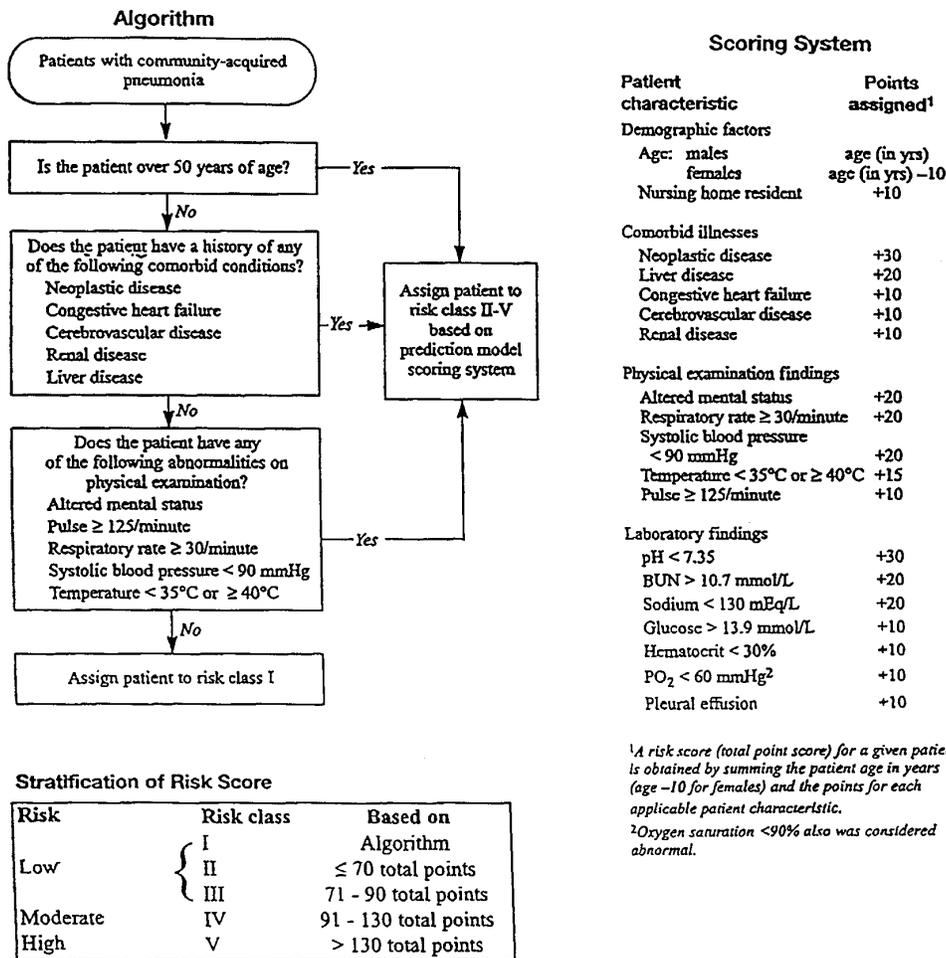


Figure 1. Prediction model for identification of patient risk for persons with community-acquired pneumonia. This model may be used to help guide the initial decision on site of care; however, its use may not be appropriate for all patients with this illness and therefore should be applied in conjunction with physician judgement. Reprinted from [9].

Comparisons of the relative frequency of each of the etiologies of pneumonia are hampered by the varying levels of sensitivity and specificity of the tests for each of the pathogens that these tests detect; for example, in some studies, tests used for legionella infections provide a much higher degree of sensitivity, and possibly, specificity, than that of tests used for pneumo-

coccal infections. Thus, the relative contribution of many causes to the incidence of CAP is undoubtedly either exaggerated or underestimated, depending on the sensitivity and specificity of tests used in each of the studies.

Etiology-Specific Diagnoses and the Clinical Setting

No convincing association has been demonstrated between individual symptoms, physical findings or laboratory test results, and specific etiology [22]. Even time-honored beliefs (e.g., the absence of a productive cough or lack of inflammatory sputum suggests etiologies such as species of *Mycoplasma*, *Legionella*, and *Chlamydia*) have not withstood close inspection. On the other hand, most comparisons have involved relatively small numbers of patients and the potential for separating causes by using constellations of symptoms and physical findings has not been evaluated. In one as yet unconfirmed study comparing patients identified in a prospective standardized fashion, a scoring system based on five symptoms and laboratory abnormalities was able to differentiate most patients with

Table 3. Risk-class mortality rates for patients with pneumonia.

Risk class	No. of points	Validation cohort		Recommendations for site of care
		No. of patients	Mortality (%)	
I	No predictors	3,034	0.1	Outpatient
II	≤70	5,778	0.6	Outpatient
III	71-90	6,790	2.8	Inpatient (briefly)
IV	91-130	13,104	8.2	Inpatient
V	>130	9,333	29.2	Inpatient

NOTE. Data are from [9].

Legionnaires' disease from the other patients [25]. A similar type of system has been devised for identifying patients with hantavirus pulmonary syndrome (HPS) [26]. If validated, such scoring systems may be useful for identifying patients who should undergo specific diagnostic tests (which are too expensive for routine use in all patients with CAP) and should be treated empirically with specific antimicrobial drugs pending the test results.

Although not absolute, certain pathogens cause pneumonia more commonly among persons with specific risk factors. For instance, pneumococcal pneumonia is classically a disease of the elderly and patients with a variety of medical conditions, including chronic cardiovascular disease, asplenia, chronic obstructive pulmonary disease (COPD), immunoglobulin deficiency, hematologic malignancy, and HIV infection. *S. pneumoniae* is second only to *P. carinii* as the most common identifiable cause of acute pneumonia in patients with AIDS [27–29]. *Legionella* is an opportunistic pathogen—Legionnaires' disease is rare among healthy young children and young adults. It is an important cause of pneumonia in organ transplant recipients and in patients with renal failure and occurs with increased frequency in patients with chronic lung disease, those who smoke, and, possibly, in those with AIDS [30]. While it has historically been believed that *M. pneumoniae* primarily involves children and young adults, recent evidence suggests that this organism causes pneumonia among healthy adults of any age [7].

There are seasonal differences in the incidence of many of the causes of CAP. Pneumonias due to *S. pneumoniae*, *H. influenzae*, and influenza virus occur predominantly in the winter months, whereas *C. pneumoniae* appears to cause pneumonias year round. While the prevalence of outbreaks of Legionnaires' disease is highest in the summer, sporadic cases of Legionnaires' disease occur with similar frequency during all seasons [7, 30]. Some studies suggest that there is no seasonal variation of mycoplasma infection; however, other data suggest that the incidence is greatest in the fall and winter months [31].

There are other temporal variations in the incidence of some causes of pneumonia. The frequency and severity of influenza vary as a result of antigenic drift and occasionally as a result of antigenic shift. For less clear reasons, increases in the incidence of mycoplasma infections occur every 3–6 years [31, 32]. Year-to-year variations may also occur with pneumococcal pneumonia. A variety of recent studies have found that the incidence of pneumococcal bacteremia may be increasing [33].

Little is known about geographic differences in the incidence of pneumonia. Passive surveillance data from the Centers for Disease Control and Prevention (CDC) suggest that the incidence of Legionnaires' disease is highest in the northeastern United States and states in the Great Lakes area [30]; however, differences in ascertainment of disease may be a contributing factor. The incidence of pneumonias due to pathogens that are environmentally related would be expected to vary along with

changes in relevant environmental conditions. For example, the incidence of Legionnaires' disease is dependent on the presence of pathogenic *Legionella* species in water, amplification of the bacteria in reservoirs with the ideal nutritional milieu, use of aerosol-producing devices that can spread contaminated water via aerosol droplets, ideal meteorological conditions for transporting aerosols to susceptible hosts, and the presence of susceptible hosts. Variations in any of these variables would likely lead to variations in incidence. Likewise, increasing rainfall with associated increases in the rodent population was hypothesized to be the basis for the epidemic of hantavirus pulmonary syndrome in the southwestern United States in 1993 [34].

Diagnostic Evaluation

Pneumonia should be suspected in patients with newly acquired lower respiratory symptoms (cough, sputum production, and/or dyspnea), especially if these symptoms are accompanied by fever, altered breath sounds, and rales. It is recognized that there must be a balance between reasonable diagnostic procedures and empirical therapy. The importance of establishing the diagnosis of pneumonia and its cause is heightened with the increasing concern for overuse of antibiotics.

Chest Radiography

The diagnosis of CAP requires a combination of clinical and laboratory (including microbiological) data. The differential diagnosis of lower respiratory tract symptoms is extensive and includes upper and lower respiratory tract infections as well as noninfectious causes (i.e., reactive airways disease, atelectasis, congestive heart failure, bronchiolitis obliterans with organizing pneumonia [BOOP], vasculitis, pulmonary embolism, and pulmonary malignancy). Most upper respiratory tract infections and acute bronchitis are of viral origin, do not require antimicrobial therapy, and are the source of great antibiotic abuse [35]. By contrast, antimicrobial therapy is usually indicated for pneumonia, and a chest radiograph is usually necessary to establish the diagnosis of pneumonia. The radiograph is occasionally useful for determining the etiologic diagnosis and the prognosis and for detecting alternative diagnoses or associated conditions. In a time of limited resources, it may be attractive to treat patients for CAP on the basis of presenting manifestations, without radiographic confirmation. However, this approach should be discouraged, given the cost and potential dangers of antimicrobial abuse in terms of side effects and resistance. Indeed, the prevalence of pneumonia among adults with respiratory symptoms suggesting pneumonitis ranges from only 3% in a general outpatient setting to 28% in an emergency department [36, 37]. The Panel recommends that a chest radiograph be obtained for the routine evaluation of patients who are likely to have pneumonia (A, II).

Decision to Hospitalize

From the standpoint of cost, the most important decision concerning the treatment of patients with CAP is whether to treat such patients as outpatients or in the hospital. A general consensus is that ~75% of patients can be appropriately treated as outpatients. Indications for admission have been summarized above with use of a constellation of clinical observations (tables 1 and 2) [9, 14, 15] combined with social and other factors [21]. Laboratory studies that are helpful for determining the severity of infection and the need for hospitalization include selected blood chemistries (i.e., glucose, blood urea nitrogen, and serum sodium levels) and pulse oximetry or arterial blood gas determinations (table 4). Other suggested routine laboratory tests include HIV serology (after informed consent is obtained) for hospitalized patients between the ages of 15 years and 54 years in hospitals where the rate of newly detected HIV infections exceeds one case per 1,000 discharges [38]. Delays in the reporting of serological results or refusal of testing may limit the timely availability of this information. Suggestive findings that support the possibility of a pulmonary complication of late-stage AIDS include the presence of lymphopenia (lymphocyte count, $<1,000/\text{mm}^3$) or, preferably, a low CD4 lymphocyte count ($\leq 200/\text{mm}^3$).

Etiology

The emphasis on microbiological studies (gram stain and culture of expectorated sputum) in the IDSA guidelines represents a difference with the ATS guidelines [1]. Arguments against microbiological studies include the low yield cited in many reports [7, 22–24] and the failure to document benefit in terms of cost or outcome. A concern of the Panel is our perception that the quality of microbiological technology, as applied to respiratory secretions, has deteriorated substantially compared with that of an earlier era [10]. Furthermore, it is our perception that regulations from the Clinical Laboratory Improvement Act contributed to this decline despite justification that was based on quality improvement. With regard to the failure to document benefit, the Panel agrees that no studies have clearly demonstrated the cost-effectiveness or other advantages of attempts to identify etiologic pathogens, but conclusions on this point are not possible because there are no studies specifically designed to address this issue. Our rationale for preserving microbiological and immunologic testing is summarized in table 5. The desire to identify the etiologic agent is heightened by concern for empirical selection of drugs due to increasing microbial resistance to drugs, unnecessary costs, and avoidable side effects. In addition, the work of prior investigators to identify pulmonary pathogens provides the information considered essential to write guidelines.

A detailed history can be important in the evaluation of CAP and may be helpful in making a diagnosis. Epidemiological

clues that may lead to diagnostic considerations are listed in table 6. Certain findings have historically been identified as clues to specific causes of pneumonia. Acute onset, single shivering chill (rigor), and pleurisy are common features of *S. pneumoniae* pneumonia. Hyponatremia, and possibly markedly elevated temperature ($>103^\circ\text{F}$) and headache, may be suggestive of legionella infection. A prodromal fever and myalgia followed by pulmonary edema and hypotension are characteristic of the hantavirus pulmonary syndrome. Underlying COPD is more often seen in patients with bacterial pneumonia, and the presence of putrid sputum suggests anaerobic infection. While many studies of CAP have found that clinical features often cannot be used to distinguish etiologic agents [22, 39, 40], others support the utility of clinical clues in establishing an etiologic diagnosis [25, 41].

Once the clinical diagnosis of CAP has been made, consideration should be directed towards the microbiological diagnosis [42–46]. Practice standards for collection, transport, and processing of respiratory secretions to detect common bacterial pathogens are summarized in table 7. Many pathogens require specialized tests for detection, and these tests are summarized in table 8. The routine rapid diagnostic test is gram staining of respiratory secretions, usually expectorated sputum; other tests include the direct fluorescent antibody (DFA) stain of sputum or the urinary antigen assay for *Legionella* (for use in selected cases) and the acid-fast stain for detection of mycobacterial infections. Many rapid diagnostic tests such as PCR assays are early in development, not commonly available, or not sufficiently accurate [50]. PCR for detection of *Mycobacterium tuberculosis* is the only PCR assay for detection of a respiratory tract pathogen that has been cleared by the U.S. Food and Drug Administration (FDA), but this assay is recommended for use only with specimens showing acid-fast bacilli on direct smear. Diagnostic procedures that provide identification of a specific etiology within 24–72 hours can still be useful for guiding continued therapy.

The etiologic diagnosis can be useful for both prognostic and therapeutic purposes. As noted previously, several studies have shown that the mortality associated with CAP among hospitalized patients is the same for those with and without etiologic diagnoses [51–55]. This finding has been used subsequently to justify empirical treatment with no attempt to identify a pulmonary pathogen. The problem with this conclusion is that there have been no studies specifically designed to test the hypothesis. Instead, the conclusion is based on retrospective analyses of cases with and without etiologic diagnoses [42]. Other outcomes that are also of interest and that have not been assessed are length-of-stay, cost, resource utilization, and morbidity. Some studies, though uncontrolled, have suggested the benefit of these diagnostic studies [56–59]. For example, Gleckman et al. [58] reported that an early diagnosis based on sputum gram-stain results correlated with a more rapid resolution of a patient's fever after initiation of antimicrobial therapy.

Table 4. Diagnostic studies for evaluation of community-acquired pneumonia.

<ul style="list-style-type: none"> • Baseline assessment Chest radiography to substantiate diagnosis of pneumonia, detect associated lung diseases, as baseline to assess response, to predict pathogen, and to assess severity • Outpatients Sputum gram stain is desirable; culture for conventional bacteria is optional • Inpatients Complete blood count with differential Chemistry panel, including glucose and serum sodium levels; liver function tests; and renal function tests, with or without electrolyte levels HIV serology with informed consent for persons aged 15–54 years in hospitals with more than one newly diagnosed case of HIV infection per 1,000 discharges Blood gases Pretreatment blood cultures (twice) Gram stain and culture of sputum* Test for <i>Mycobacterium tuberculosis</i> with acid-fast stain and culture for selected patients, especially those with cough for >1 month, other common symptoms, or suggestive radiographic changes Test for Legionnaires' disease for selected patients, including all seriously ill patients without an alternative diagnosis, especially if >40 years of age, immunocompromised, nonresponsive to β-lactam antibiotics, has clinical features suggesting this diagnosis, or in outbreak settings Tests for <i>Mycoplasma pneumoniae</i> and <i>Chlamydia pneumoniae</i> (not routinely recommended because of limitations in sensitivity, specificity, and availability) Thoracentesis with stain, culture, pH determination, leukocyte count, and leukocyte count with differential • Alternative specimens to expectorated sputum Aspirates from intubated patients, tracheostomies, and nasotracheal aspirates (manage as with expectorated sputum) Induced sputum (recommended for detection of <i>M. tuberculosis</i> or <i>Pneumocystis carinii</i>) Bronchoscopy (recommended primarily for detection of <i>M. tuberculosis</i> in patients who cannot produce expectorated sputum, for detection of <i>P. carinii</i> in the absence of expectorated sputum showing PMNs, and in selected cases of enigmatic pneumonia, especially when unresponsive to standard therapy; for immunocompromised patients; and when bronchoscopy is done for other indications.) Routine bronchoscopy specimens are considered comparable to expectorated sputum for detection of conventional pathogens. Quantitative cultures of BAL fluid or protected brush specimens improve specificity, if done using techniques with established merit. Transtacheal aspiration (recommended only in cases of enigmatic pneumonia and should be performed by persons skilled in the technique, preferably before antibiotic treatment) Transthoracic needle aspiration (recommended only in cases of enigmatic pneumonia and should be performed by persons skilled in the technique, preferably before antibiotic treatment) • Optional Additional cytologic or microbiological tests, as listed in table 7, depending on clinical features, available resources, underlying conditions and/or epidemiological associations of the patient Serum—to be frozen and saved for serologic analysis if needed[†]

NOTE. BAL = bronchoalveolar lavage; PMNs = polymorphonuclear neutrophils.

* Should be a deep-cough specimen obtained before antibiotic therapy. Gram stain should be interpreted by trained personnel, and culture should be done only if specimen is adequate by cytological criteria, except for *Legionella* and mycobacteria. Consider diagnostic studies for endemic fungi and mycobacteria when clinical features suggest these diagnoses. For hospitalized patients with severe pneumonia or clinical features suggesting Legionnaires' disease, perform culture and urine antigen assay. The inability to obtain specimens for diagnostic studies should not delay antibiotic treatment of acutely ill patients.

[†] Serological tests would include those for *M. pneumoniae*, *Legionella pneumophila*, *C. pneumoniae*, or other organisms (i.e., viruses, *Chlamydia psittaci*, or *Coxiella burnetii*), depending on the circumstances.

An additional study by Torres et al. [59] showed that inadequate antibiotic treatment was clearly related to poor outcomes, and this finding suggests that the establishment of an etiologic diagnosis is important.

It is our consensus that establishment of an etiologic diagnosis has value for patients requiring hospitalization (B, II). The goal is a specific diagnosis allowing for more precise and often

more cost-effective use of antimicrobial agents. On the other hand, the utility of diagnostic studies for CAP of less severity (not requiring hospitalization) is unclear. More studies are needed to verify the significance of diagnostic studies in such cases.

Confidence in the accuracy of the diagnosis depends on the pathogen and on the diagnostic test as follows:

Table 5. Rationale for establishing an etiologic diagnosis for patients with community-acquired pneumonia.

To permit optimal antibiotic selection in terms of activity against a specific pathogen (this especially applies to penicillin-resistant *Streptococcus pneumoniae*)

To permit antibiotic selection that limits the consequences of antibiotic abuse in terms of cost, resistance, and adverse drug reactions

To identify pathogens of potential epidemiological significance such as *Legionella*, Hantavirus, and penicillin-resistant *S. pneumoniae*

The average cost of standard microbiological studies is <1% of the average hospital bill

Although many reports indicate that the yield of pathogens in expectorated sputum from patients with CAP is only 30% to 40%, this yield may often be increased with improved techniques; furthermore, a negative specimen may enhance the probability of an atypical agent (which may influence the antimicrobial treatment decision), and a good-quality specimen that does not show or yield *Staphylococcus aureus* or gram-negative bacilli provides good evidence that these organisms are not present. This information may prove useful for patients who do not respond to treatment, since conventional cultures of posttreatment specimens are relatively useless.

NOTE. CAP = community-acquired pneumonia.

(1) *Etiologic diagnosis definite*: A compatible clinical syndrome plus recovery of a likely etiologic agent from an uncontaminated specimen (blood, pleural fluid, a transtracheal aspirate, or a transthoracic aspirate) or recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *M. tuberculosis*, *Legionella* species, influenza virus, or *P. carinii*) (table 9; A, I). Some serological tests are regarded as diagnostic, although the results are usually not available in a timely manner or the diagnostic criteria are controversial.

(2) *Etiologic diagnosis probable*: A compatible clinical syndrome with detection (by stain or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, a bronchoscopic aspirate, or a bronchoalveolar lavage (BAL) or brush-catheter specimen that has been cultured). With semi-quantitative culture, the pathogen should be recovered in moderate to heavy growth (B, II).

The following specimens are used to establish an etiologic diagnosis:

(1) *Body fluids*: Blood for culture should be obtained (at least two times with needlesticks at separate sites) from patients who require hospitalization for acute pneumonia (B, III). Prior studies have indicated that an average of 11% of hospitalized patients with CAP have positive blood cultures [7]. Other potentially infected body fluids, including pleural fluid, joint fluid, and CSF, should be gram stained and cultured.

(2) *Sputum examination* (table 7 and figure 2): The value of a gram stain of expectorated sputum has been debated [41, 43, 44, 51–53, 58–62], but we recommend a relatively simple,

inexpensive procedure as a guide to initial selection of antimicrobial therapy, with the following caveats: a deep cough specimen is obtained before initiation of antibiotic therapy, it is rapidly transported, and it is properly processed in the laboratory within 1–2 hours of collection (B, II). Treatment of acutely ill patients with antimicrobial agents should not be delayed because of difficulty in obtaining specimens for microbiological studies. Routine laboratory tests should include gram staining, cytological screening, and aerobic culture of specimens that satisfy cytological criteria. Cytological criteria for acceptability are based on the relative number of polymorphonuclear cells and squamous epithelial cells (SECs) in specimens from patients with normal or elevated WBC counts, as determined by using low-power-field (LPF) microscopy; some authorities consider <25 SECs per LPF to be an appropriate minimal criterion based on correlation of culture of screened specimens

Table 6. Epidemiological and underlying conditions related to specific pathogens in selected patients with community-acquired pneumonia.

Condition	Commonly encountered pathogens
Alcoholism	<i>Streptococcus pneumoniae</i> , anaerobes, gram-negative bacilli
COPD/smoker	<i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Legionella</i> species
Nursing-home residency	<i>S. pneumoniae</i> , gram-negative bacilli, <i>H. influenzae</i> , <i>Staphylococcus aureus</i> , anaerobes, <i>Chlamydia pneumoniae</i>
Poor dental hygiene	Anaerobes
Epidemic Legionnaires' disease	<i>Legionella</i> species
Exposure to bats or soil enriched with bird droppings	<i>Histoplasma capsulatum</i>
Exposure to birds	<i>Chlamydia psittaci</i>
Exposure to rabbits	<i>Francisella tularensis</i>
HIV infection (early stage)	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Mycobacterium tuberculosis</i>
Travel to the southwestern United States	<i>Coccidioides immitis</i>
Exposure to farm animals or parturient cats	<i>Coxiella burnetii</i> *
Influenza active in community	Influenza, <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>Streptococcus pyogenes</i> , <i>H. influenzae</i>
Suspected large-volume aspiration	Anaerobes, chemical pneumonitis
Structural disease of the lung (bronchiectasis or cystic fibrosis)	<i>Pseudomonas aeruginosa</i> , <i>Burkholderia (Pseudomonas) cepacia</i> , or <i>S. aureus</i>
Injection drug use	<i>S. aureus</i> , anaerobes, <i>M. tuberculosis</i>
Airway obstruction	Anaerobes

NOTE. COPD = chronic obstructive pulmonary disease.

* Agent of Q fever.

Table 7. Recommendations for expectorated sputum collection, transport, and processing.

1. The specimen should be obtained by deep cough and be grossly purulent; it should be obtained before treatment with antimicrobial agents and in the presence of a physician or nurse.
2. The specimen should be immediately transported to the laboratory for prompt processing. Delays of 2–5 hours at room temperature result in reduced isolation rates for *Streptococcus pneumoniae*, *Staphylococcus aureus*, and gram-negative bacilli with increased numbers of indigenous flora [47].
3. A purulent portion is selected for gram stain and culture. Quellung test should be done when available.
4. Cytological screening should be done under low-power magnifications ($\times 100$) to determine the cellular composition. Criteria for culture are variable: the “classic study” required < 10 SECs and > 25 PMNs per LPF [48]. Investigators have shown that < 10 SECs per LPF was an appropriate criterion; others conclude that < 25 SECs per LPF should represent a minimum criterion based on correlation with TTA results [49]. Cytological assessment is not useful for screening specimens for detection of *Legionella* or mycobacteria.
5. Culture should be performed by using standard techniques and reporting with semiquantitative assessment. Most pathogens are recovered in 3–4 + growth, indicating more than five colonies in the second streak.

NOTE. LPF = low-power field; PMN = polymorphonuclear neutrophils; SECs = squamous epithelial cells; TTA = transtracheal aspirate.

compared with transtracheal aspiration (A, I) [48, 49]. Mycobacteria and *Legionella* species are exceptions, since cytological criteria may give misleading results. Gram stains should be performed rapidly to reduce unnecessary delays in therapy. Cultures should also be performed rapidly to improve accuracy; delays from the time of specimen collection to incubation that exceed 2–5 hours may be associated with deceptive results [47]. Interpretations of expectorated sputum culture results should include clinical correlations and semiquantitative results. In office practices, it may not be realistic to prepare a gram stain in a timely manner to guide antibiotic decisions, but a slide may be prepared, air dried, and heat fixed for subsequent interpretation (C, III).

The limitations of these recommendations are that many patients cannot produce good specimens and have often received antimicrobial agents before evaluation, and the results with many specimens are inconclusive. Nevertheless, the results of multiple studies support the utility of routine sputum bacteriology, with recognition of lancet-shaped gram-positive diplococci suggesting infection due to *S. pneumoniae*. Most studies have shown that the sensitivity of sputum gram stains for patients with pneumococcal pneumonia is 50%–60% and that the specificity is $> 80\%$ [41, 44–46, 58]. In addition, Gleckman et al. [55] found that by using blood culture isolates as a standard of reference and by using selectively defined criteria for the validity of sputum specimens, the sensitivity of a “positive” gram stain was 85% and physicians could have

selected appropriate antimicrobial therapy for $> 90\%$ of patients on the basis of gram stain results. In that prospective study of 144 patients admitted to the hospital with CAP, 59 (41%) were found to have valid specimens with the cytologic criteria of > 25 polymorphonuclear cells and < 10 SECs per LPF. The gram stains of 47 valid specimens, based on these criteria, showed a predominant bacterial morphotype that predicted the blood culture isolate in 40 (85%). The validity of a gram stain, however, is directly related to the experience of the interpreter [63].

Routine cultures of expectorated sputum are neither sensitive nor specific when they are performed by using the common bacteriologic methods available in many laboratories. Problems include antecedent antibiotic exposure, poor-quality specimens, delays in processing, and difficulty with interpretation because of contamination by the flora of the upper airways. The flora may include potential pathogens (false-positive cultures), and the normal flora often overgrows the true pathogen (false-negative cultures), especially in the case of fastidious pathogens such as *S. pneumoniae*; in cases of bacteremic pneumococcal pneumonia, *S. pneumoniae* may be isolated from a sputum culture in only 40%–50% of cases when standard microbiological techniques are used [64, 65]. Optimal detection is achieved with mouse inoculation, use of a dissecting microscope to examine culture plates, and rapid plating after specimen collection.

The yield of *S. pneumoniae* is substantially higher in cultures of transtracheal aspirates [66–69] and transthoracic needle aspirates [67, 70] and in quantitative cultures of BAL aspirates [71]. The relatively low yield of *S. pneumoniae* from expectorated sputum is at least partially explained by the lack of strict adherence to quality assurance for expeditious transport and processing of specimens. Prior antibiotic therapy significantly reduces the yield of common respiratory pathogens from cultures of respiratory tract specimens from any source, and prior therapy is often associated with false-positive cultures for upper airway contaminants such as gram-negative bacilli or *S. aureus* [43, 67]. The concern over false-negative cultures after antibiotic therapy is particularly great with respect to common fastidious pathogens such as *S. pneumoniae* or *H. influenzae*.

(3) *Induced sputum*: This method of obtaining sputum is generally recommended for detection of *P. carinii* and for detection of *M. tuberculosis* in patients who cannot provide expectorated sputum samples [67]. The utility of this method in the detection of other pulmonary pathogens is poorly established.

(4) *Serological studies*: These tests are usually not helpful in the initial evaluation of patients with CAP (C, III), but they may provide data that are useful for epidemiological surveillance. The presence of cold agglutinins at a titer of $\geq 1:64$ supports the diagnosis of *M. pneumoniae* infection with a sensitivity of 30%–60%, but agglutination assays have poor specificity. Up to 1 week is required for IgM antibodies to

Table 8. Diagnostic studies for specific agents of community-acquired pneumonia.

Pathogen	Rapid diagnostic test(s)*	Standard culture or microbiologic test(s)	Serology, other tests or finding
Aerobic bacteria and facultative anaerobes <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> Gram-negative bacilli <i>Staphylococcus aureus</i> Other	Gram stain morphology	ES, US, [†] bronchoscopy	...
Obligate anaerobes <i>Mycoplasma pneumoniae</i>	Gram stain morphology PCR [‡]	US [†] Throat or nasopharyngeal swab (rarely done, requires specialized culture techniques)	... ELISA, CF, agglutination assay
<i>Chlamydia pneumoniae</i>	PCR [‡]	Throat or nasopharyngeal swab (rarely done, requires specialized culture techniques)	Microimmunofluorescence
<i>Chlamydia psittaci</i>		Usually not done (considered laboratory hazard)	CF
<i>Legionella</i> species	Urine antigen assay (for <i>Legionella pneumophila</i> serogroup 1), PCR, [†] DFA of respiratory secretions, lung tissue, or pleural fluid (primarily for <i>L. pneumophila</i> serogroup 1; some false-positives with other serogroups and species)	ES or IS, US, [†] bronchoscopy	IFA (reciprocal immunofluorescence titer of ≥ 128 for <i>Legionella</i> serogroup 1; single IFA titer lacks specificity)
<i>Nocardia</i> species	Gram stain morphology Modified carbol-fuchsin stain	ES, US, [†] bronchoscopy	
<i>Coxiella burnetii</i> Mycobacteria species	Acid-fast stain (fluorochrome or carbol-fuchsin), PCR [‡]	ES or IS, US, [†] bronchoscopy	CF
Pathogenic fungi <i>Histoplasma capsulatum</i>	GMS or calcofluor white stain	ES or IS, US, [†] bronchoscopy	CF, immunodiffusion, antigen assay (blood, urine, respiratory secretions) for <i>Histoplasma capsulatum</i> antigen
<i>Coccidioides immitis</i>	Calcofluor white stain or KOH with phase contrast	ES or IS, US, [†] bronchoscopy	CF
<i>Blastomyces dermatitidis</i>	Calcofluor white stain or KOH with phase contrast	ES or IS, US, [†] bronchoscopy	
<i>Cryptococcus neoformans</i>	Calcofluor white or GMS stain, antigen assay (serum)	ES or IS, US, [†] bronchoscopy	ELISA or LA for serum antigen
Opportunistic <i>Candida</i> species	Gram stain	US, [†] histology of biopsy	Histology required to implicate <i>Candida</i> species
<i>Aspergillus</i>	GMS or calcofluor white stain	Respiratory secretion—stain results, US, [†] histology of biopsy specimen	For allergic bronchopulmonary aspergillosis, serology; septate hyphal elements in respiratory secretions suggest <i>Aspergillus</i>
Zygomycetes	GMS or calcofluor white stain	Respiratory secretion—stain results, US, [†] histology of biopsy specimen	Nonseptate large hyphal elements in respiratory secretions suggest Zygomycetes
<i>Pneumocystis carinii</i>	GMS, Giemsa, or DFA stain	IS, bronchoscopy (yield much higher)	
Viruses			
Influenza	Antigen detection (EIA), DFA stain	Virus isolation, nasopharyngeal swab	CF or HAI
RSV	Antigen detection (EIA), DFA stain	Virus isolation, nasopharyngeal washing	
Adenovirus	DFA stain, PCR [‡]	Virus isolation, pharyngeal swab	ELISA or RIA

Table 8. (Continued)

Pathogen	Rapid diagnostic test(s)*	Standard culture or microbiologic test(s)†	Serology, other tests or finding
Parainfluenza	DFA stain	Virus isolation, pharyngeal swab	
Varicella	Clinical—associated with skin manifestations	Virus isolation	CF (negative acute)
Herpes simplex virus	Typical cytopathology	Virus isolation	Histopathology (preferred)
Cytomegalovirus	Typical cytopathology of respiratory secretions (usually via bronchoscopy)	Incubation (24 h) using shell vial methodology, DFA stain, or immunofluorescence of peripheral WBCs	Histopathology (preferred)
Hantavirus (see text)	PCR‡	...	Complete blood count, ELISA for IgG and IgM, immunohistochemistry for antigen

NOTE. DFA = direct fluorescent antibody; ES = expectorated sputum; GMS = Grocott-Gomori methenamine silver stain; HAI = hemagglutination inhibition; IS = induced sputum; IFA = indirect fluorescent antibody; KOH = potassium hydroxide; LA = latex agglutination; RAI = radioimmunoassay; US = uncontaminated specimens.

* Respiratory secretions unless otherwise stated.

† Pleural fluid, blood, transtracheal aspirate, transthoracic aspirate, or lung biopsy specimen.

‡ PCR is available in selected reference laboratories, but reagents for detecting *M. pneumoniae* and *C. pneumoniae* are not FDA cleared (PCR is FDA cleared for detection of *M. tuberculosis* in specimens that are acid-fast stain positive).

M. pneumoniae to reach diagnostic titers, and these titers persist for 2–12 months. The serological responses to *Chlamydia* and *Legionella* take longer; therefore testing of acute-phase sera is not usually helpful when therapeutic decisions must be made.

Table 9. Diagnostic value of microbial pathogens recovered from respiratory secretions in patients with community-acquired pneumonia.

Pathogenic role definite, regardless of specimen source	Pathogenic role not definite if recovered from usual respiratory specimens*
<i>Legionella</i> species	Virtually all other bacteria, including <i>Nocardia</i> species and <i>Actinomyces</i> species
<i>Mycobacterium tuberculosis</i>	Mycobacteria other than <i>M. tuberculosis</i>
Viruses	
Influenza virus	Cytomegalovirus
Respiratory syncytial virus	Herpes simplex virus
Hantavirus	
Parainfluenza virus	
Coxsackievirus	
Adenovirus	
Parasites	—
<i>Strongyloides stercoralis</i>	
<i>Toxoplasma gondii</i>	
Fungi	
<i>Pneumocystis carinii</i>	<i>Candida</i> species
<i>Histoplasma capsulatum</i>	<i>Aspergillus</i> species
<i>Coccidioides immitis</i>	Zygomycetes
<i>Blastomyces dermatitidis</i>	<i>Cryptococcus neoformans</i>

* Sputum, bronchoalveolar lavage fluid, or nasotracheal aspirate.

The relative merits of various tests for *C. pneumoniae* (microimmunofluorescence serology, PCR, or culture) [72] have been debated, and few diagnostic microbiology laboratories offer any of these tests. In primary infection due to *C. pneumoniae*, IgM antibodies may take up to 3 weeks to appear, and IgG antibodies may take up to 8 weeks to appear [73]. Therefore, the absence of detectable antibodies (even IgM) several weeks

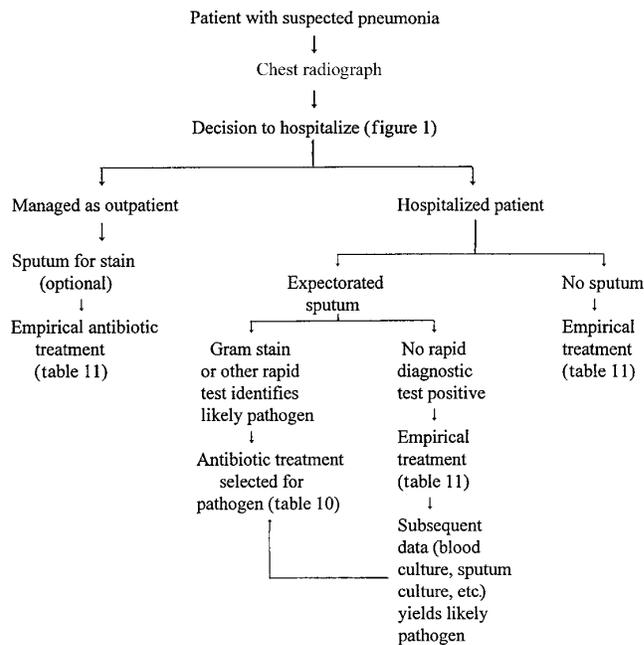


Figure 2. Flow chart approach to treating outpatients and inpatients with community-acquired pneumonia.

after infection does not exclude the diagnosis of acute *C. pneumoniae* infection. During reinfection, the IgG antibody level rises rapidly, while the IgM antibody level may not change.

A test for antibodies to *Legionella* in the acute phase of Legionnaires' disease is usually negative or shows a low titer [74, 75]. Some authorities have accepted an acute-phase titer of $\geq 1:256$ as a criterion for a probable or presumptive diagnosis, but one study showed that this titer had a positive predictive value of only 15% [75]. IgM antibodies develop concurrently with IgG antibodies, thus limiting their utility in detecting acute infection. Ideally, an acute-phase serum specimen should be obtained from selected patients with CAP and stored. If the etiology of a case remains in question, a convalescent-phase serum specimen can be obtained, and paired serological studies can be performed. This method for identifying Legionnaires' disease retrospectively is primarily for epidemiological information. The above data indicate that there are no commonly available serological tests that can be used to accurately guide therapy for acute infections caused by *M. pneumoniae*, *C. pneumoniae*, or *Legionella* species (D, III).

(5) *Antigen detection*: Antigen detection methods for identifying microorganisms in sputum and in other fluids have been studied for >70 years with a variety of techniques: counterimmunoelectrophoresis, latex agglutination, immunofluorescence, and EIA. While the use of these techniques for detecting bacterial agents (i.e., *S. pneumoniae*) has been favored in many European centers, their use has been less acceptable in North American laboratories. Cost, time requirements, and relative lack of sensitivity and specificity (depending upon the method) are potential limitations. The Quellung test for *S. pneumoniae* is an exception, with the proviso that there is adequate expertise. Rapid, commercially available EIAs are available for the detection of influenza virus; respiratory syncytial virus (RSV); adenovirus; and parainfluenza viruses 1, 2, and 3. The sensitivities of these tests are >80%.

Urine antigen tests have been shown to be sensitive and specific for detecting *Legionella pneumophila* serogroup 1, which accounts for ~70% of reported cases of Legionnaires' disease in the United States [30]; other possible advantages of these tests are the technical ease of performing them and the validity of results after several days of effective antibiotic treatment. DFA staining of respiratory secretions is technically demanding, yields optimal results with *L. pneumophila*, and has poor sensitivity and specificity when not performed by experts using only certain antibodies. Culture and urine antigen tests have sensitivities of 50%–60% and >95% specificity. A negative laboratory test does not exclude Legionnaires' disease, particularly if it is caused by organisms other than *L. pneumophila* serogroup 1, but a positive culture or urine antigen assay is virtually diagnostic. To detect Legionnaires' disease, the Panel recommends urine antigen assays and sputum culture on selective and nonselective media with specimen decontamination before plating (A, II).

(6) *DNA probes and amplification*: Several rapid diagnostic tests with use of nucleic acid amplification for the evaluation of respiratory secretions or serum are presently under development, especially for detecting species of *Chlamydia*, *Mycoplasma*, and *Legionella* [50]. The reagents for these tests have not been approved by the FDA, and their availability is generally restricted to research and reference laboratories [50, 72]. If such tests become available, they may be extremely helpful in establishing early diagnoses and allowing directed therapy at the time of care. Their greatest potential utility is anticipated for the detection of *M. pneumoniae*, *Legionella* species, and selected pathogens that infrequently colonize the upper airways in the absence of disease (table 7).

(7) *Invasive diagnostic tests—transtracheal aspiration (TTA), bronchoscopy, and percutaneous lung needle aspiration (PLNA) (table 3)*: TTA was previously used to obtain uncontaminated lower respiratory secretions that were valid for culture of anaerobic organisms and common aerobic pathogens [43, 67]. This procedure is now infrequently performed because of concern for adverse effects and lack of personnel skilled in the technique. A consequence of the reduced use of TTA is the lack of any method for detecting anaerobic bacteria in the lung when empyema or bacteremia are absent.

The utility of fiberoptic bronchoscopy varies depending on the pathogen and the technique. Because aspirates obtained from the inner channel of the bronchoscope are subject to contamination by the upper airway flora, they should not be cultured anaerobically, and they have the same diagnostic limitations as expectorated sputum [67, 76]. For recovery of common bacterial pathogens, quantitative culture of BAL fluid or a protected brush catheter specimen is considered superior [77, 78]. The techniques for collection, transport, and processing of specimens for quantitative culture have been published [67, 77, 78]. Bronchoscopy is impractical for routine use because it is expensive, requires technical expertise, and may be difficult to perform in a timely manner. Some authorities favor its use in patients with fulminant clinical courses who require admission to the intensive care unit or have complex pneumonias that are unresponsive to antimicrobial therapy [11, 67, 71, 79]. Bronchoscopy is especially useful for detecting selected pathogens such as *P. carinii*, *Mycobacterium* species, and cytomegalovirus. Most investigators view this procedure as relatively risk-free for selected patients, especially those who are compromised [67]. For detection of AFB, specimens obtained by bronchoscopy offer no clear advantage over expectorated sputum or induced sputum, but bronchoscopy is advocated for patients who are suspected of having mycobacterial infection and who cannot produce sputum, and it adds to the total yield along with induced sputum [80].

PLNA has been used primarily for cytological evaluation of suspected neoplasms or for the investigation of pulmonary infiltrates in immunocompromised patients. The use of this technique for diagnosing the etiology of CAP has been limited

in the past because of potential complications, especially bleeding and pneumothorax. The more recent introduction of thinner needles has reduced the frequency of complications. The diagnostic yield ranges from ~40% to 80% [67, 70]. This technique is often preferably performed under fluoroscopic guidance. Contraindications include the presence of bullous pulmonary disease in the area requiring aspiration, a suspected vascular lesion, a bleeding disorder, inability to cooperate, and intractable cough (a relative contraindication). Limitations of PLNA include the small specimen volume obtained and the possibility of improper needle placement, leading to false-negative results [70].

The Panel recommends that only blood cultures and gram staining and culture of expectorated sputum be considered the routine microbiological studies for patients hospitalized with CAP. TTA, transthoracic needle aspiration, and bronchoscopy should be reserved for selected patients and then used only with appropriate expertise (B, III).

Diagnostic Approach—Recommendations

Table 4 lists diagnostic studies recommended for hospitalized patients, according to the severity of illness (B, II).

Special Considerations

Pneumococcal Pneumonia

S. pneumoniae is among the leading infectious causes of illness and death worldwide for young children, persons who have underlying chronic systemic conditions, and the elderly. A meta-analysis of 122 reports of CAP that were published in the English-language literature from 1966 through 1995 showed that *S. pneumoniae* accounted for 66% of >7,000 cases in which an etiologic diagnosis was made and that it also accounted for ~66% of lethal pneumonias [8]. It has been estimated that 500,000 cases of pneumococcal pneumonia occur annually in the United States. A vaccine for the most common serotypes of *S. pneumoniae* is available, and the Advisory Committee on Immunization Practices recommends that the vaccine be administered to all persons ≥ 65 years of age and to younger persons who have underlying medical conditions associated with an increased risk for pneumococcal disease and its complications [81].

Until recently in the United States, *S. pneumoniae* was nearly uniformly susceptible to penicillin; this circumstance allowed clinicians to treat patients with severe pneumococcal infection with penicillin G alone, without testing for drug susceptibility. Resistance of *S. pneumoniae* to penicillin and to other antimicrobial drugs, first noted in Australia and Papua New Guinea in the 1960s, spread to South Africa in the 1970s and subsequently to many countries in Europe, Africa, and Asia in the 1980s.

In the United States, nonsusceptibility to penicillin has increased markedly during the last decade [33, 82, 83]. The prevalence of resistance varies sharply by geographic region and can change rapidly over time [83]; a survey in 1994 of 1,527 isolates from 30 centers showed that 24% of pneumococci had reduced susceptibility to penicillin, including 10% that had high-level resistance (MIC, ≥ 2 $\mu\text{g}/\text{mL}$) [83]. The MICs for most strains with high-level resistance are 2–4 $\mu\text{g}/\text{mL}$. Strains with reduced susceptibility to penicillin are often resistant to other β -lactams, trimethoprim-sulfamethoxazole, macrolides, and other antibiotics. In some communities, a smaller, but still substantial percentage of isolates are resistant to multiple drugs commonly used to treat CAP.

A survey of 720 isolates of *S. pneumoniae* from 11 states in 1993–1994 showed that 89% of 128 strains that were nonsusceptible to penicillin were of serotypes included in the 23-valent vaccine [33]. Members of the Panel are not aware of clinical failures of penicillin treatment for pneumococcal pneumonia that have been ascribed to in vitro resistance, and one report has shown a lack of clinical correlation with in vitro susceptibility test results for patients treated with penicillin or cephalosporins [84]. For strains that show intermediate resistance (MIC, 0.1–1.0 $\mu\text{g}/\text{mL}$), parenteral penicillin or oral amoxicillin continue to be considered appropriate therapies, although oral cephalosporins and macrolides may be inadequate for these strains. The same concern regarding lack of correlation between in vitro and in vivo results applies to treatment of infections due to strains with high-level resistance (MIC, ≥ 2 $\mu\text{g}/\text{mL}$), but in this setting we advocate alternative agents that are more predictably active or have demonstrated in vitro activity.

Initial treatment for pneumococcal pneumonia is empirical because rapid, sensitive, and specific susceptibility tests are not available. Excessive use of antimicrobial drugs and use of inappropriate empirical or prophylactic agents contribute to the spread of drug-resistant *S. pneumoniae* by providing drug-resistant organisms a selective advantage. Optimally, the choice of antimicrobial drug to treat pneumococcal pneumonia should be guided by local or regional prevalence of drug-resistant *S. pneumoniae*. Since the prevalence of resistance to penicillin and other drugs in most communities is currently unknown, many states are implementing surveillance for drug-resistant pneumococcal infections, so that community-specific data may become available soon.

In accordance with the standards of the National Committee for Clinical Laboratory Standards, all isolates of *S. pneumoniae* from usually sterile sites (e.g., blood or CSF) should be tested for penicillin resistance (B, III). A 1- μg oxacillin disk can be used to screen for penicillin nonsusceptibility (>99% sensitivity and 80% specificity). When isolates are found to be nonsusceptible by use of the oxacillin disk method, the MICs of penicillin, cefotaxime or ceftriaxone, tetracyclines, chloramphenicol, vancomycin, fluoroquinolones, and other drugs for

such isolates should be determined. Some authorities believe that use of the oxacillin disk for screening is no longer justified because of the high rate of penicillin resistance and the resulting day of delay in reporting results. Reliable methods for MIC testing include broth microdilution, antimicrobial gradient strips (Etest; AB BIODISK, Solna, Sweden), and agar dilution. As of this writing, automated tests are unacceptably insensitive for detecting drug resistance and should not be used for pneumococcal drug susceptibility testing.

Because the diagnosis of pneumococcal disease is based on the isolation of *S. pneumoniae* from respiratory secretions more frequently than from blood, members of the IDSA Panel recommend that respiratory isolates be subjected to the same antimicrobial susceptibility testing as described above for blood and CSF isolates when *S. pneumoniae* is clinically suspected to be the cause of pneumonia (B, III). Since the results of antimicrobial susceptibility testing will typically not be available for 2–3 days after specimens have been collected, the results of susceptibility testing should be used to narrow the choice for antimicrobial treatment when possible by eliminating broad-spectrum and multiple drugs that may have initially been administered empirically. It should be emphasized again that the clinical implications of in vitro penicillin resistance of *S. pneumoniae*, in terms of antibiotic selection, are not yet clear. The Panel endorses the use of parenteral penicillin G or oral amoxicillin as preferred agents for susceptible strains (MIC, <0.1 µg/mL). For strains with intermediate susceptibility (MIC, 0.1–1 µg/mL), parenteral penicillin/amoxicillin or alternative agents are preferred; for strains with high-level penicillin resistance (MIC, ≥2 µg/mL), alternative agents such as vancomycin or fluoroquinolones or other agents that are active in vitro are preferred. Strains that are nonsusceptible to penicillin are often resistant to macrolides and oral cephalosporins; thus these agents must be used with caution when selected empirically.

Aspiration Pneumonia

Aspiration pneumonia is broadly defined as the pulmonary sequela of the entry of material from the stomach or upper respiratory tract into the lower airways. The term generally applies to large-volume aspiration. There are at least three distinctive forms of aspiration pneumonia [85], according to the nature of the inoculum, the clinical presentation, and management guidelines: toxic injury of the lung (such as gastric acid aspiration or Mendelson's syndrome), obstruction (foreign body or fluids), or infection (table 10). These syndromes are reviewed elsewhere [86, 87]. Most studies have shown that 5%–10% of patients hospitalized with CAP are suspected of having aspirated, although the criteria for this diagnosis are often not provided. In general, the diagnosis should be suspected for patients who have a predisposing cause for aspiration (usually compromised consciousness or dysphagia) and radiographic evidence of involvement of a dependent pulmonary

segment (the lower lobes are dependent in the upright position, and the superior segments of the lower lobes and posterior segments of the upper lobes are dependent in the recumbent position). Aspiration pneumonia is the presumed cause of nearly all cases of anaerobic pulmonary infections.

Anaerobic Bacterial Infections

The frequency of anaerobic infection among patients with CAP is not known because the methods required to obtain valid, uncontaminated specimens for meaningful anaerobic culture are rarely used. The usual specimens are transtracheal aspirates, pleural fluid, transthoracic needle aspirates, and uncontaminated specimens from sites of metastasis [67, 88]; limited experience suggests that quantitative cultures of protected brush or BAL specimens collected at bronchoscopy may be acceptable [67, 77, 78, 88, 89]. The results of prior studies suggest that anaerobic bacteria are the most common etiologic agents of lung abscess and aspiration pneumonia, and these bacteria are relatively common isolates in cases of empyema [87]. Patients with anaerobic bacterial infection may also present with pneumonitis, which on the basis of clinical features, is indistinguishable from other common forms of bacterial pneumonia [90]. Clinical clues to the diagnosis of anaerobic infection include a predisposition to aspiration, infection of the gingival crevice (gingivitis), putrid discharge, necrosis of tissue with abscess formation or a bronchopulmonary fistula, infection complicating airway obstruction, chronic course, and infection in a dependent pulmonary segment [87]. Some studies have suggested that anaerobes may also account for a substantial number of cases of CAP that do not have these characteristic features [77, 91].

The only comparative therapeutic trials for anaerobic lung infections have been conducted in patients with lung abscess, and these trials have shown that clindamycin is superior to iv penicillin [92, 93]. The use of metronidazole as a single agent has resulted in a high treatment failure rate, presumably because of the role played by aerobic and microaerophilic streptococci. Other regimens that appear effective are metronidazole plus penicillin and amoxicillin/clavulanate (A, I) [94]. Antibiotics that are virtually always active against anaerobes in vitro include imipenem, meropenem, chloramphenicol, and any combination of a β-lactam–β-lactamase inhibitor. Macrolides, cephalosporins, and doxycycline show variable activity; trimethoprim-sulfamethoxazole, aminoglycosides, and the currently available fluoroquinolones other than trovafloxacin are not active against most anaerobes.

The Panel recommends clindamycin as the preferred drug for treating pulmonary infections when anaerobic bacteria are established or suspected as the cause; alternative options are metronidazole plus penicillin and amoxicillin/clavulanate (B, I).

Table 10. Characteristics of different forms of aspiration pneumonia.

Inoculum	Pulmonary sequelae	Clinical features	Therapy
Acid	Chemical pneumonitis	Acute dyspnea, tachypnea, tachycardia; possible cyanosis, bronchospasm, or fever; pink, frothy sputum; infiltrates in one or both lower lobes; hypoxemia	Positive-pressure breathing, intravenous fluids, tracheal suction
Oropharyngeal bacteria	Bacterial infection	Usually insidious onset; cough, fever, purulent sputum; infiltrate involving dependent pulmonary segment or lobe, with or without cavitation	Antibiotics
Inert fluids	Mechanical obstruction, reflex airway closure	Acute dyspnea, cyanosis with or without apnea; pulmonary edema	Tracheal suction, intermittent positive-pressure breathing with oxygen and isoproterenol
Particulate matter	Mechanical obstruction	Dependent on level of obstruction, ranging from acute apnea and rapid death to irritating chronic cough with or without recurrent infections	Extraction of particulate matter, antibiotics for superimposed infection

C. pneumoniae Pneumonia

Although the prevalence of CAP varies from year to year and within geographical settings, studies indicate that ~5%–15% of cases are caused by *C. pneumoniae* [7, 22–24, 95–97]. The clinical spectrum of CAP ranges from asymptomatic infection to life-threatening pneumonia; however, the majority of cases of pneumonia due to *C. pneumoniae* are relatively mild and are associated with low mortality [95, 96]. *C. pneumoniae* pneumonia may present as sore throat, hoarseness, and headache as important nonpneumonic symptoms; other findings include sinusitis, reactive airways disease, and empyema. Reinfection is common, and hospitalization due to pneumonia caused by *C. pneumoniae* is usually required for older patients who have reinfection in which comorbidities undoubtedly play a significant role in the clinical course. *C. pneumoniae* is often found in association with other pathogens, particularly *S. pneumoniae*, and the associated pathogen appears to influence the clinical course of the pneumonia [95].

Infection can be suspected on the basis of culture of *C. pneumoniae*, DNA detection, PCR, and serology (most specifically, by detection of microimmunofluorescent antibodies) [47, 72, 95–97]. However, cell culture is not routinely available except in research laboratories; PCR technology is not standardized, the reagents for PCR are not FDA cleared, and serology is problematic because it is nonspecific [47, 98]. The preferred diagnostic test is assay of acute and convalescent specimens to detect a fourfold increase in antibody titers, with supporting evidence based on PCR or culture results. With the current limitations in diagnostic testing, most laboratories will not be able to confirm or exclude a diagnosis of *C. pneumoniae* pneumonia in a timely fashion; therefore, treatment must be empirical (A, II). For therapy the Panel recommends macrolides and tetracycline (including doxycycline), as well as some of

the fluoroquinolones (ofloxacin, levofloxacin, or sparfloxacin) on the basis of available data (B, II) [96, 99].

Legionnaires' Disease

Legionella species are implicated in 2%–6% of CAP cases in most hospital-based series; some groups report higher rates that presumably reflect local epidemiology and/or superior laboratory techniques [7, 22–24, 100]. Risk is related to exposure, increasing age, smoking, and compromised cell-mediated immunity such as that in transplant recipients [30]. Although rare in immunocompetent adults of <30 years of age, legionellosis can be a major cause of lethal pneumonia, with mortality rates of 5%–25% among immunocompetent hosts and substantially higher rates among immunosuppressed hosts [30, 100]. Diagnostic testing is arbitrary in terms of indications and choice of tests (table 7). Tests commonly cost \$50 to \$100 each, and therefore, routine testing of hospitalized patients is not usually advocated.

Major indications for testing hospitalized patients include the following: severe illness requiring admission to the intensive care unit, lack of any other likely etiology except *Legionella* species (i.e., a gram stain is negative), pneumonia in a compromised host, evidence that *Legionella* species are endemic or epidemic in the area, lack of response to β -lactam antibiotics, or clinical features suggesting *Legionella* as the cause (C, III) [74]. Epidemiological risk factors for Legionnaires' disease include recent travel with an overnight stay outside the home, recent repair of domestic plumbing, renal or hepatic failure, diabetes, or systemic malignancy [30]. Some investigators believe that the following clinical features suggest the diagnosis of Legionnaires' disease: high fever, hyponatremia, CNS manifestations, lactate dehydrogenase levels of

>700 U/mL, or the presence of severe disease [100]. Methods of laboratory detection include culture, serology, DFA stain, urine antigen assay, and PCR. DFA stains require substantial expertise for interpretation, and selection of reagents is critical. PCR is expensive, and there are no FDA-approved reagents. Tests recommended by the Panel are a urine antigen assay for *L. pneumophila* serogroup 1, a test that is technically non-demanding and that reliably and rapidly detects up to 70% of cases of Legionnaires' disease, and culture on selective media, which detects all *Legionella* strains but is technically demanding [30, 100, 101] (B, II).

Historically, the preferred therapy has been erythromycin, usually in a dose of 2–4 g/d, given intravenously, with or without oral rifampin (300 mg b.i.d. or 600 mg q.d.); treatment can be changed to oral erythromycin (500 mg q.i.d. for a total of 2–3 weeks of treatment) when there is clinical response. Many investigators now consider azithromycin and fluoroquinolones (ciprofloxacin, ofloxacin, or levofloxacin) to be preferred for severe disease, based in part on the superior results obtained when these agents were compared to erythromycin in animal models [30, 100, 102, 103]. FDA-approved drugs for Legionnaires' disease are erythromycin, intravenous azithromycin, levofloxacin, and dirithromycin. A delay in therapy is associated with increased mortality [104]. The Panel considers doxycycline, azithromycin, ofloxacin, ciprofloxacin, and levofloxacin to be preferred for Legionnaires' disease on the basis of available data (B, II). These drugs are available for oral and parenteral administration. The duration of treatment should be 10–21 days (less for azithromycin because of its long half-life).

Hantavirus Pulmonary Syndrome

This frequently lethal systemic disease of previously healthy young adults was originally recognized in May 1993. At least five viruses in the Hantavirus genus are implicated, the most common of which is Sin Nombre (SN) virus [105]. The primary host for SN virus is the deer mouse *Peromyscus maniculatus*, which apparently remains healthy but sheds the virus in urine, stool, and saliva. The usual mechanism of transmission is by aerosolization. Cases of HPS have been reported in nearly every region of the United States, but most cases have been found in the Four Corners area (New Mexico, Arizona, Utah, and Colorado). The median age of the patients with the first hundred cases in the United States was 35 years, and the overall case fatality rate was 52% [106].

Common features of the prodromal phase include fever, chills, myalgias, headache, nausea, vomiting, and/or diarrhea. A cough is common but is not a prominent early feature. Initial symptoms resemble those of other common viral infections. Characteristic features often become evident after the 3–6 day prodrome and include characteristic laboratory changes, a chest radiograph showing capillary leakage (adult respiratory distress

syndrome [ARDS]), and oxygen desaturation. Other more common causes of ARDS that should be considered are chronic pulmonary disease, malignancy, trauma, burns, and surgery. Among lethal cases of HPS, the median time to death is 5 days after disease onset. Typical laboratory findings include hemoconcentration, thrombocytopenia, leukocytosis with a left shift, and circulating immunoblasts. Additional laboratory findings include an elevated serum lactate dehydrogenase level, an arterial PO₂ level of <90 mm Hg, and an increased serum lactate level.

The diagnosis is established by detection of hantavirus-specific IgM or rising titers of hantavirus-specific IgG, detection of hantavirus-specific RNA by PCR in clinical specimens, or detection of hantavirus antigen by immunohistochemistry [101, 106]. These laboratory tests should be performed, or the results confirmed, at a reference laboratory. Treatment consists largely of supportive care, often requiring intubation and mechanical ventilation with positive end-expiratory pressure. Patients also require hemodynamic support. Ribavirin inhibits SN virus in vitro, but the initial clinical experience with this drug has been disappointing.

M. pneumoniae Pneumonia

M. pneumoniae is a common cause of respiratory tract infections, primarily in the age group of 5–9 years and in young adults; the frequency among older adults requiring hospitalization for CAP is reported to range from 2% to 30% [2, 7, 8, 22–24, 31, 32]. The incubation period is 2–4 weeks; thus epidemics in closed populations evolve slowly. The most common presentation is tracheobronchitis; ~3% of patients have clinically evident pneumonia that is usually established with chest radiography. Common symptoms in cases of pneumonia include a prodromal period with fever, chills, headache, and sore throat; these symptoms are followed by a cough that is dry or productive of mucoid sputum [31, 107]. The cough is frequently most severe at night and may persist for 3–4 weeks. A possible clue to this diagnosis is a history of contact with a person with a similar condition characterized by a long incubation period. Extrapulmonary manifestations may include cold hemagglutination and hemolytic anemia, nausea and vomiting, myocarditis, rash, and diverse neurological syndromes.

Laboratory tests to confirm infection due to *M. pneumoniae* include culture for *Mycoplasma*, serological tests, and PCR [32, 50, 72]. Fastidious growth requirements and long incubation periods limit the utility of culture, and most laboratories do not offer this test. Titers of IgM and IgG antibodies become elevated in most cases, but the response is often delayed so that the utility of these tests for early detection is also limited. Some authorities consider PCR to be particularly promising [50]. Current problems with amplification techniques include great variability due to differences in methods of sample collection, sample preparation, and amplification procedure; there are

also no FDA-cleared reagents with which to perform PCR for *Mycoplasma* detection. Cold agglutinin titers of $\geq 1:64$ support the diagnosis, and the cold agglutinin response correlates with the severity of pulmonary symptoms; however, the test lacks specificity.

It has been suggested that a single CF antibody titer of $\geq 1:64$, combined with a cold agglutinin titer of $\geq 1:64$, is strongly supportive of this diagnosis [31, 32]. The antibody response usually develops 7–10 days after the onset of symptoms and shows peak levels at ~ 3 weeks. Changes on chest radiographs are nonspecific; the most common change is a unilateral infiltrate, but one-third of patients have bilateral changes.

Members of the Panel have concluded that there is no diagnostic test that will reliably and rapidly detect *M. pneumoniae* infection and that is readily available to most laboratories. Thus, therapy must usually be empirical (B, II). The Panel recommends treatment with tetracycline or a macrolide for most cases; an alternative is the fluoroquinolones (B, III). Treatment should be given for 2–3 weeks to reduce the risk of relapse. The role of antibiotic therapy for extrapulmonary manifestations has not been established.

***Pneumocystis carinii* Pneumonia (PCP)**

PCP is not included in the guidelines for management of CAP in immunocompetent hosts because PCP is seen exclusively in patients with defective cell-mediated immunity. Nevertheless, this is a relatively common and important form of pneumonia, especially in patients with HIV infection who may not have had the underlying defect in host defenses recognized at the time of presentation. One recent study of 385 consecutive hospitalizations for CAP in an urban hospital showed that 46% of patients had HIV infection and that 19% of these patients were unaware of their HIV status at the time of admission [24]. The point to emphasize is that PCP is the most common initial AIDS-defining diagnosis and should be suspected in selected patients, even in the absence of known immunodeficiency.

Characteristic clinical features of PCP include a nonproductive cough, fever, and dyspnea that evolve over a period of weeks. The average patient complains of pulmonary symptoms that have been present for ~ 4 weeks at the time of initial presentation; this relatively slow progression of disease is a characteristic feature that distinguishes PCP from common forms of bacterial pneumonia in patients with AIDS. The usual associated laboratory features include lymphopenia (total lymphocyte count, $< 1,000/\text{mL}$), CD4 lymphopenia (CD4 lymphocyte count, $< 200/\text{mL}$ in $> 95\%$ of patients), arterial hypoxemia, and a chest radiograph that shows bilateral interstitial infiltrates with a highly characteristic “ground-glass” appearance. Up to 30% of patients have unremarkable chest radiographs, making this illness the only relatively common form of pneumonia associated with false-negative chest radiographs

[108]. The diagnostic yield with induced sputum averages 60% but varies greatly, depending on quality control [109]. The yield with bronchoscopy exceeds 95%.

The disease is uniformly fatal if not treated. Trimethoprim-sulfamethoxazole, dapsone/trimethoprim, and clindamycin/primaquine appear to be equally effective for treatment of patients who have moderately severe disease [110]. No treatment currently recommended by these or other guidelines for the immunocompetent host with pneumonia is likely to be effective for PCP. (This statement applies to trimethoprim-sulfamethoxazole as well because of differences in dosage). The mortality rate among treated patients who are hospitalized has usually been reported to be 15%–20%.

Influenza

In terms of morbidity and mortality, influenza is clearly the most serious viral airway infection of adults. Seasonal epidemics are commonly associated with $\geq 20,000$ deaths in the United States that are ascribed to this infection and its complications, primarily bacterial superinfections. The great pandemics of influenza in the past century were the “Spanish flu” of 1918 that was responsible for > 20 million deaths worldwide, the Asian influenza of 1957, and the Hong Kong influenza of 1968. Analysis of historical records, molecular epidemiological findings, and seroarcheology suggests that there will be another influenza pandemic among humans, but the time has not been predicted [111].

The majority of patients who die during annual influenza epidemics are > 65 years of age, a disproportionate number of whom are residents of chronic care facilities. The most common cause of bacterial superinfection is *S. pneumoniae* and, to a lesser extent, *S. aureus* [112]. In general, influenza A is more severe and shows greater antigenic heterogeneity than influenza B. Treatment with amantadine or rimantidine appears to reduce symptoms in patients with influenza A, but it is not clear that this treatment reduces mortality rates or complications such as bacterial superinfections [113].

Annual administration of vaccine provides the most effective prophylaxis, usually with an efficacy of 60%–70% for prevention of transmission. Efficacy for prevention is reduced in elderly residents of chronic care facilities, but the effectiveness in preventing death is often reported to be 70%–80% in this population, depending to some extent on the match between the epidemic strain and the constituents of the vaccine [114]. A recent provocative report suggests that vaccination of health care providers in chronic care facilities is as important or more important than vaccination of the patients [115]. These data emphasize the importance of vaccine strategies that target the populations at greatest risk, including persons aged 65 years or older, patients with cardiopulmonary disease, and residents of nursing homes and their care providers (A, I).

Empyema

The traditional definition of pleural empyema is pus in the pleural space. More recently, investigators have performed pleural fluid analyses; a pleural effusion with a pH of <7.2 usually indicates a need for drainage [116]. The frequency of this complication among patients with CAP that is sufficiently severe to require hospitalization is reported to be 1%–2% [8]. The incidence of empyema has decreased substantially from the preantibiotic era, when *S. pneumoniae* accounted for about two-thirds of cases, and the bacteriology has changed as well. A meta-analysis of 1,289 cases of empyema reported from 1970 to 1995 showed that *S. pneumoniae* now accounts for only 5%–10% of cases; the majority involve anaerobic bacteria, *S. aureus*, and/or gram-negative bacilli [117]. Many cases of empyema are mixed infections, and many are culture negative, findings that suggest the use of inadequate culture techniques or the impact of prior antibiotic treatment.

Most studies of CAP show that up to 57% of patients with CAP have pleural effusions identified on routine chest radiographs [118]. Empyema is infrequent in these patients, but it is important to recognize the condition because of its implications regarding the need for adequate drainage, a critical component of effective management. Some authorities recommend thoracentesis for any parapneumonic effusion that measures >10 mm on a lateral decubitus radiograph [118]. Standard tests to be performed on pleural fluid include appropriate stains and culture for aerobic and anaerobic bacteria; measurement of pH, the lactate dehydrogenase level, and the leukocyte count; and determination of the differential. Particularly important is the pH, which requires the same handling as a specimen for an arterial blood gas determination: fluid is obtained anaerobically, placed on ice, and the pH is measured in a radiometer system. Pus in the pleural space requires drainage; a positive culture or a pH of <7.2 usually will require drainage. Neither the lactate dehydrogenase or glucose levels are as sensitive as pH for this prediction.

Drainage is not necessary for uncomplicated parapneumonic effusions, e.g., free-flowing fluid with a pH of >7.3 . Parapneumonic effusions for which gram stains or cultures are positive or those with a pH of <7.2 will usually require drainage. Pleural pus always requires drainage. The drainage technique may be by chest tube, image-guided catheters, thoracoscopy, or thoracotomy. The relative merits and indications for image-guided catheters, catheters with thrombolytics, and thorascopic or thoracotomy decortication are not well defined.

Management

Management recommendations within this document are restricted to immunocompetent adults with acute CAP in two settings: those treated as outpatients and those who are hospitalized (figure 2). Emphasis should be accorded to the following:

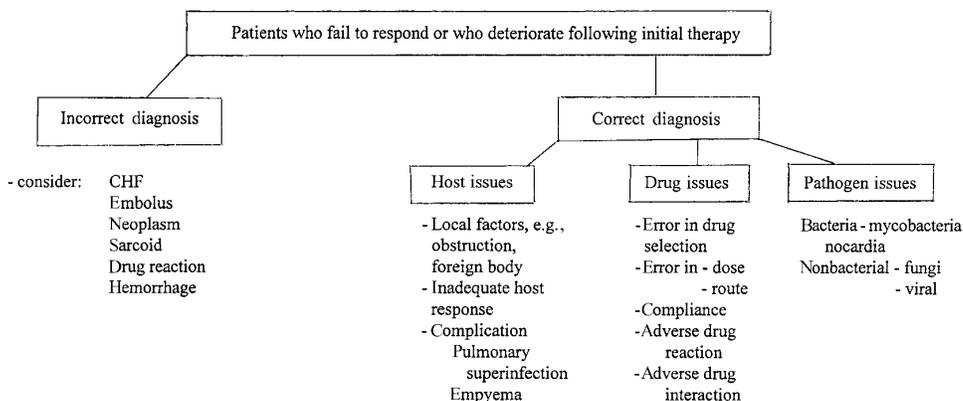
1. *Rational use of the microbiology laboratory.* Patients who are candidates for hospitalization with acute pneumonia should have blood cultures performed and a physician-procured expectorated sputum specimen obtained before antimicrobials are administered unless these procedures would delay initiation of treatment (B, II). Consensus as to the need for obtaining microbiological diagnoses for outpatients is lacking, although it is desirable to prepare an air-dried, heat-fixed slide of sputum for subsequent gram staining before antimicrobial treatment is started. Investigation for selected microbial pathogens such as *Legionella* and mycobacteria will depend on clinical features.
2. *An attempt should be made to administer pathogen-directed antimicrobial therapy to hospitalized patients* (C, III) (table 11). This decision should be made when relevant information becomes available, and its strength is greatest in cases where an established etiologic agent has been identified according to the criteria described above. When necessary, empirical agents should be chosen that are directed against the pathogens that are most common and treatable according to the setting (table 12). Antibiotic regimens selected empirically should be changed in light of culture and in vitro susceptibility test results when this information becomes available, on the assumption that clinical and microbiological correlations support this tactic.
3. *Antimicrobial treatment should be initiated promptly* after the diagnosis of pneumonia is established on the basis of radiographic findings and gram stain results are available to facilitate antimicrobial selection. For patients requiring hospitalization for acute pneumonia, it is important to initiate therapy in a timely fashion; there is at least one analysis of 14,000 patients that showed that a delay from the time of admission to initiation of antibiotic treatment exceeding 8 hours was associated with an increase in mortality (B, II) [119]. Antibiotic treatment should not be withheld from acutely ill patients because of delays in obtaining appropriate specimens or the results of gram stains and cultures.
4. *Decisions regarding hospitalization should be based on prognostic criteria*, as summarized in tables 1 and 2 (A, I). In addition, this decision will be influenced by other factors such as the availability of home support, probability of compliance, and availability of alternative settings for supervised care. Many patients with CAP are hospitalized for a concurrent disease process. Prior studies have shown that 25%–50% of admissions for CAP are for these other considerations that extend beyond those listed as admission criteria in table 1 [9].

Treatment of Patients Who Do Not Require Hospitalization

Diagnostic Studies

The diagnosis of pneumonia requires the demonstration of an infiltrate on a chest radiograph. Postero-anterior and lateral

Figure 3. Possible reasons for failure of empirical treatment in patients with community-acquired pneumonia.



chest radiographs are recommended when pneumonia is suspected (A, II), although obtaining them may not always be practical. Additional diagnostic studies in patients who are candidates for hospitalization are summarized in table 4 (B, II). For patients who are not seriously ill and do not require hospitalization, it is desirable to perform a sputum gram stain, with or without culture. A complete blood count with differential is sometimes useful for further assessing the illness in terms of severity, the presence of associated conditions, or chronicity.

Pathogen-Directed Therapy

Treatment options are obviously simplified if the etiologic agent is established or strongly suspected. Antibiotic treatment decisions based on the identification of microbial pathogens are summarized in table 11 (C, III).

Empirical Antibiotic Treatment Decisions (table 12)

The selection of antibiotics in the absence of an etiologic diagnosis (gram stains and culture results are not diagnostic) is based on multiple variables including severity of the illness, patient age, antimicrobial intolerance or side effects, clinical features, comorbidities, concomitant medications, exposures, and the epidemiological setting (B, II) (table 6).

Preferred antimicrobials for most patients (in no special order): Macrolide,* fluoroquinolones,† or doxycycline

Alternative options: Amoxicillin/clavulanate and some second-generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil)

Note: These will not be active versus atypical agents.

*Macrolide: erythromycin, clarithromycin, or azithromycin; clarithromycin or azithromycin are preferred if *H. influenzae* infection is suspected.

†Fluoroquinolone: Levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae*.

Treatment of Patients Who Are Hospitalized

Diagnostic Studies

Diagnostic studies recommended for hospitalized patients are summarized in table 4 (B, II). Patients hospitalized for acute pneumonia should have blood drawn for two cultures, preferably with two separate needle sticks ≥10 minutes apart before antibiotics are administered (B, II). A deep-cough expectorated sputum sample should be obtained by a nurse or physician before antibiotics are administered (B, II). This sample should be transported to the laboratory for gram stain and culture within 1–2 hours of collection. Testing for *Legionella* species, *M. tuberculosis*, and other pathogens should be included in selected settings. Antimicrobial treatment should be initiated promptly and should not be delayed in an attempt to obtain pretreatment specimens from acutely ill patients for microbiological studies (B, III). Induced sputum samples have established value for the detection of *P. carinii* and *M. tuberculosis*, and use of such samples should be generally limited to cases with these diagnostic considerations (A, I). Bronchoscopy or bronchoscopy and quantitative cultures and other invasive diagnostic techniques should be reserved for selected clinical settings or clinical studies (B, III). Examples of clinical settings that may justify the use of bronchoscopy include pneumonia in immunosuppressed hosts, suspected tuberculosis in the absence of a productive cough, selected cases of chronic pneumonia, pneumonia associated with a suspected neoplasm or foreign body, suspected *P. carinii* pneumonia, some cases in which intubation is required, and suspected conditions that require a lung biopsy (B, II).

Preferred antimicrobials for most patients (in no special order):

General medical ward

Preferred: a β-lactam* with or without a macrolide† or a fluoroquinolone‡ (alone)

Table 11. Treatment of pneumonia according to pathogen.

Pathogen	Preferred antimicrobial	Alternative antimicrobial
<i>Streptococcus pneumoniae</i>		
Penicillin susceptible (MIC, <0.1 µg/mL)	Penicillin G or penicillin V, amoxicillin	Cephalosporins,* macrolides,† clindamycin, fluoroquinolones,‡ doxycycline
Intermediately penicillin resistant (MIC, 0.1–1 µg/mL)	Parenteral penicillin G, ceftriaxone or cefotaxime, amoxicillin, fluoroquinolones,‡ other agents based on in vitro susceptibility test results	Clindamycin, doxycycline, oral cephalosporins*
Highly penicillin resistant§ (MIC, ≥2 µg/mL)	Agents based on in vitro susceptibility results, fluoroquinolones,‡ vancomycin	
Empirical selection	Fluoroquinolones;‡ selection based on susceptibility test results in community Penicillin#	Clindamycin, doxycycline, vancomycin Cephalosporins,* macrolides,† amoxicillin, clindamycin
<i>Haemophilus influenzae</i>	Second- or third-generation cephalosporins, doxycycline, β-lactam–β-lactamase inhibitor, fluoroquinolones‡	Azithromycin, TMP-SMZ
<i>Moraxella catarrhalis</i>	Second- or third-generation cephalosporins, TMP-SMZ, amoxicillin/clavulanate	Macrolides,† fluoroquinolones,‡ β-lactam–β-lactamase inhibitor
Anaerobes	Clindamycin, penicillin plus metronidazole, β-lactam–β-lactamase inhibitor	Penicillin G or penicillin V, ampicillin/ amoxicillin with or without metronidazole
<i>Staphylococcus aureus</i> §		
Methicillin susceptible	Nafcillin/oxacillin with or without rifampin or gentamicin§	Cefazolin or cefuroxime, vancomycin, clindamycin, TMP-SMZ, fluoroquinolones‡
Methicillin resistant	Vancomycin with or without rifampin or gentamicin	Requires in vitro testing; TMP-SMZ
Enterobacteriaceae (coliforms: <i>Escherichia coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Enterobacter</i>)§	Third-generation cephalosporin with or without an aminoglycoside, carbapenems**	Aztreonam, β-lactam–β-lactamase inhibitor, fluoroquinolones‡
<i>Pseudomonas aeruginosa</i> §	Aminoglycoside plus antipseudomonal β-lactam: ticarcillin, piperacillin, mezlocillin, ceftazidime, cefepime, aztreonam, or carbapenems**	Aminoglycoside plus ciprofloxacin, ciprofloxacin plus antipseudomonal β-lactam
<i>Legionella</i> species	Macrolides† with or without rifampin, fluoroquinolones‡	Doxycycline with or without rifampin
<i>Mycoplasma pneumoniae</i>	Doxycycline, macrolides,† fluoroquinolones‡	...
<i>Chlamydia pneumoniae</i>	Doxycycline, macrolides,† fluoroquinolones‡	...
<i>Chlamydia psittaci</i>	Doxycycline	Erythromycin, chloramphenicol
<i>Nocardia</i> species	Sulfonamide with or without minocycline or amikacin, TMP-SMZ	Imipenem with or without amikacin, doxycycline or minocycline
<i>Coxiella burnetii</i> ††	Tetracycline	Chloramphenicol
Influenza A	Amantadine or rimantadine	
Hantavirus	None‡‡	

NOTE. TMP-SMZ = trimethoprim-sulfamethoxazole.

* Intravenous: cefazolin, cefuroxime, cefotaxime, ceftriaxone; oral: cefpodoxime, cefprozil, cefuroxime.

† Erythromycin, clarithromycin, or azithromycin.

‡ Levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae*; ciprofloxacin is appropriate for *Legionella* species, fluoroquinolone-susceptible *S. aureus*, and most gram-negative bacilli.

§ In vitro susceptibility tests are required for optimal treatment; for *Enterobacter* species, the preferred antibiotics are fluoroquinolones and carbapenems.

|| High rates of high-level penicillin resistance, susceptibility of community strains unknown, and/or patient is seriously ill.

Low rates of penicillin resistance in community and patient is at low risk for infection with resistant *S. pneumoniae*.

** Imipenem and meropenem.

†† Agent of Q fever.

‡‡ Provide supportive care.

Table 12. Empirical antibiotic selection for patients with community-acquired pneumonia.

Outpatients
Generally preferred: Macrolides,* fluoroquinolones, [†] or doxycycline
Modifying factors
Suspected penicillin-resistant <i>Streptococcus pneumoniae</i> : fluoroquinolones [†]
Suspected aspiration: amoxicillin/clavulanate
Young adult (>17–40 y): doxycycline
Hospitalized patients
General medical ward
Generally preferred: β -lactam [‡] with or without a macrolide* or a fluoroquinolone [†] (alone)
Alternatives: cefuroxime with or without a macrolide* or azithromycin (alone)
Hospitalized in the intensive care unit for serious pneumonia
Generally preferred: erythromycin, azithromycin, or a fluoroquinolone [†] plus cefotaxime, ceftriaxone, or a β -lactam- β -lactamase inhibitor [§]
Modifying factors
Structural disease of the lung: antipseudomonal penicillin, a carbapenem, or cefepime plus a macrolide* or a fluoroquinolone [†] plus an aminoglycoside
Penicillin allergy: a fluoroquinolone [†] with or without clindamycin
Suspected aspiration: a fluoroquinolone plus either clindamycin or metronidazole or a β -lactam- β -lactamase inhibitor [§] (alone)

* Azithromycin, clarithromycin, or erythromycin.

[†] Levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae*.

[‡] Cefotaxime, ceftriaxone, or a β -lactam- β -lactamase inhibitor.

[§] Ampicillin/sulbactam, or ticarcillin/clavulanate, or piperacillin/tazobactam (for structural disease of the lung, ticarcillin/clavulanate or piperacillin).

Alternatives: cefuroxime with or without a macrolide[†] or azithromycin (alone)

Hospitalized in intensive care unit

Preferred: erythromycin, azithromycin, or a fluoroquinolone[†] plus cefotaxime, ceftriaxone, or a β -lactam- β -lactamase inhibitor[§]

Modifying factors

Structural disease of lung (bronchiectasis): antipseudomonal penicillin, carbapenem, or cefepime plus a macrolide[†] or fluoroquinolone[†] plus an aminoglycoside

Penicillin allergy: fluoroquinolone[†] with or without clindamycin

Suspected aspiration: fluoroquinolone[†] plus clindamycin or a β -lactam- β -lactamase inhibitor[§]

* β -lactam: cefotaxime or ceftriaxone

[†]Macrolide: azithromycin, clarithromycin, or erythromycin

[‡]Fluoroquinolone: levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae*

[§] β -lactam- β -lactamase inhibitor: ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam; for structural disease of the lung: ticarcillin/clavulanate or piperacillin/clavulanate

Antibiotic Considerations

Antibiotics are the mainstay of treatment for most patients with pneumonia. Guidelines for the selection of regimens are summarized in tables 11 (B, II) and 12 (B, II) and are based largely on clinical experience and/or in vitro activity. Other important considerations in antibiotic selection concern patient tolerance, ease of administration, breadth of spectrum, and cost. Treatment options are simplified if a likely etiologic diagnosis is established or highly suspect on the basis of results of rapid tests such as a gram stain, other special stains, antigen detection, or amplification techniques (table 11). The selection of agents is based on multiple variables including severity of illness, patient age, antimicrobial tolerability or side effects, clinical features, comorbidity, exposures, and epidemiological setting (table 6) and prevalence of drug resistance among respiratory tract pathogens. Suggested regimens for empirical use in patients hospitalized for acute pneumonia are summarized in table 12, with a distinction between regimens for general use and regimens for patients who require treatment in the intensive care unit (B, II). The following discussion reviews salient relevant issues with respect to the use of these drugs in pneumonic patients.

β -lactams and related agents. All β -lactams exert their antibacterial effects by interfering with synthesis of the peptidoglycan component of the bacterial cell wall. The β -lactams are inactive against all strains of *M. pneumoniae* and *C. pneumoniae*, and they are ineffective in the treatment of legionella infections. The penicillins vary from narrow-spectrum agents with activity largely limited to gram-positive cocci (i.e., penicillin G, penicillin V, and oxacillin) to expanded-spectrum agents with activity against many gram-negative bacilli (e.g., piperacillin, ticarcillin, and mezlocillin). Parenteral penicillin G and oral penicillin V or amoxicillin are generally viewed as the β -lactam drugs of choice for treating infections with penicillin-susceptible strains of *S. pneumoniae*. Lung infections involving strains with intermediate susceptibility to penicillin (MIC, 0.1–1.0 μ g/mL) may be treated with parenteral penicillin G or, for ambulatory patients, oral amoxicillin. Alternatives to penicillin are generally preferred for infections involving *S. pneumoniae* resistant to penicillin (MIC, ≥ 2 μ g/mL). Penicillins combined with β -lactamase inhibitors (amoxicillin/clavulanate, ticarcillin/clavulanate, ampicillin/sulbactam, and piperacillin/tazobactam) are active against β -lactamase-producing organisms including *H. influenzae*, anaerobes, *Moraxella catarrhalis*, and methicillin-susceptible strains of *S. aureus*. These drugs offer no advantage over penicillin G for the treatment of *S. pneumoniae* infections, including those due to penicillin-

resistant strains, because β -lactamase is not produced by *S. pneumoniae*.

Cephalosporins. These drugs generally show enhanced activity against aerobic gram-negative bacilli as one moves from first- to second- to third-generation agents. The agents in this class most active against strains of *S. pneumoniae* are cefotaxime and ceftriaxone [33, 82, 83], and the clinical relevance of in vitro resistance to these drugs is unclear [84]. The rank order of in vitro activity of oral cephalosporins against *S. pneumoniae* is as follows: cefpodoxime \geq cefuroxime $>$ cefprozil \geq cefixime $>$ cefaclor = loracarbef $>$ cefadroxil = cephalexin [83]. The clinical implications of these in vitro data are unclear, but none of these oral agents have established clinical efficacy in cases involving strains of *S. pneumoniae* with reduced penicillin susceptibility. Most second- and third-generation cephalosporins show moderate-to-good activity against *H. influenzae* and *M. catarrhalis*; activity against *S. aureus* is variable; cefazolin and cefuroxime are the most active, and cefixime and ceftazidime are the least active. Cephalosporins with the best in vitro activity against anaerobic gram-negative bacilli (*Prevotella* and *Bacteroides* species) are cefoxitin, cefotetan, and cefmetazole, although there are no published studies of the use of these drugs for anaerobic lung infections. Other cephalosporins are less active in vitro against anaerobes.

Carbapenems. Meropenem and imipenem are active against a broad spectrum of aerobic and anaerobic gram-positive and gram-negative organisms including most strains of *S. pneumoniae*, most *P. aeruginosa* isolates, and virtually all strains of *H. influenzae*, *M. catarrhalis*, anaerobes, and methicillin-susceptible *S. aureus*. Activity against penicillin-resistant *S. pneumoniae* is generally good.

Macrolides. Erythromycin has a limited spectrum of activity and is poorly tolerated because of gastrointestinal side effects. Newer macrolides that are better tolerated but more expensive include azithromycin and clarithromycin. All three drugs appear to be effective in the treatment of pulmonary infections caused by *M. pneumoniae*, *C. pneumoniae* and *Legionella* species. Approximately 10%–15% of *S. pneumoniae* isolates are resistant to macrolides in vitro; this rate is substantially higher among penicillin-resistant strains [33, 82, 83], so that caution is necessary when these agents are used empirically in suspected cases of pneumococcal pneumonia. Activity against anaerobes, except for fusobacteria, is reasonably good. Community-acquired strains of *S. aureus* are usually susceptible to macrolides. Most bacteria are susceptible or resistant to all three macrolides, but there are some differences. Erythromycin is relatively inactive against *H. influenzae*. Clarithromycin also has relatively limited in vitro activity against *H. influenzae*; however, its 14-OH metabolite augments the activity of the parent compound [120]. Of the three macrolides, azithromycin is the agent most active in vitro against *Legionella* species, *H. influenzae*, and *M. pneumoniae*, whereas clarithromycin is the most active against *S. pneumoniae* and *C. pneumoniae*.

Azithromycin and erythromycin are available for intravenous administration. A recent multicenter, prospective study of 864 immunocompetent outpatients with CAP showed that erythromycin is cost-effective antimicrobial therapy [121].

Quinolones. The currently available agents in this class for treatment of pulmonary infections are ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin. The latter four agents were introduced in 1997. These drugs are active in vitro against most clinically significant aerobic gram-positive cocci, gram-negative bacilli, *H. influenzae*, *M. catarrhalis*, *Legionella* species, *M. pneumoniae*, and *C. pneumoniae*. Ofloxacin, levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin show enhanced in vitro activity against *S. pneumoniae* (including penicillin-resistant strains) [33], and initial clinical trials have shown good results [122, 123], although there is limited published experience with these drugs in patients with serious CAP or serious pneumococcal pneumonia.

Ciprofloxacin is slightly less active in vitro, and there are anecdotal reports of clinical failures with this drug in the treatment of pneumococcal pneumonia; some authorities believe that a dose of 750 mg twice daily would be adequate for empirical use. Activity against *S. aureus* is somewhat variable because of increasing resistance; in general, *S. aureus* strains resistant to one fluoroquinolone are resistant to all members of the class. In terms of differences, ciprofloxacin and trovafloxacin are the quinolones most active against *P. aeruginosa*, and trovafloxacin is the most active against anaerobes [123]. Excessive and inappropriate use of drugs in this group is a concern because increases in the MICs of ofloxacin (and presumably, other fluoroquinolones) for sequentially collected strains of *S. pneumoniae* have been observed [82]. Ciprofloxacin, ofloxacin, levofloxacin, and trovafloxacin are available for intravenous administration.

Aminoglycosides. The aminoglycosides (gentamicin, tobramycin, netilmicin, and amikacin) show a concentration-dependent bactericidal effect, permitting a single daily dose regimen. These agents are active in vitro against the aerobic and facultative gram-negative bacilli, including *P. aeruginosa*, and also exhibit activity against methicillin-susceptible *S. aureus* [124]. Aminoglycosides should not be used as single agents for treatment of gram-negative bacillary pneumonia. The poor clinical results may be due to low levels of drug obtainable in situ after intravenous injection and the possibility that the drug is inactivated by the acidic environment present at the site of infection [125, 126].

Tetracyclines. There are multiple members of this class, but the one most frequently used in clinical practice today is doxycycline because of its tolerability, good bioavailability, and low price and because of the convenience of twice-daily dosing. From the point of view of respiratory tract pathogens, the tetracyclines are active in vitro against the atypical organisms including *M. pneumoniae*, *C. pneumoniae*, and *Legionella*

species [127]. In the past, *S. pneumoniae* and *H. influenzae* have been quite susceptible to these agents, but there is concern about occasional resistance, including resistance in *S. pneumoniae* in 5%–8% of isolates [33, 82, 83, 128, 129].

Vancomycin. This drug is the only currently available agent with universal activity against *S. pneumoniae* [33, 83]. It is also active against other gram-positive organisms including methicillin-resistant *S. aureus*.

Clindamycin. Clindamycin exhibits good in vitro activity against gram-positive cocci, including most strains of *S. pneumoniae* (including most penicillin-resistant and most macrolide-resistant strains) and most isolates of methicillin-susceptible *S. aureus* [83, 130]. Many authorities consider clindamycin to be the preferred drug for treatment of anaerobic pulmonary infections including aspiration pneumonia and putrid lung abscess [87, 92, 93]. The drug is inactive against *H. influenzae*, atypical agents, and most erythromycin-resistant *S. aureus* strains.

Trimethoprim-sulfamethoxazole. This combination is active in vitro against a broad spectrum of gram-positive and gram-negative bacteria, although there is growing concern over increasing resistance, particularly among strains of *S. pneumoniae* and *H. influenzae* [33, 83]. Approximately 15%–20% of *S. pneumoniae* strains are resistant to trimethoprim-sulfamethoxazole, and >50% of penicillin-resistant *S. pneumoniae* are not susceptible to trimethoprim-sulfamethoxazole [33, 83]. This drug is active against such diverse pathogens as *Nocardia asteroides*, *P. carinii*, and *Stenotrophomonas maltophilia* [129, 131].

Length and Route of Treatment

We are not aware of any controlled trials that have specifically addressed the questions of how long pneumonia should be treated. This decision is usually based on the pathogen, response to treatment, comorbid illness, and complications. It is known, for example, that relapses of *C. pneumoniae* infection may occur when erythromycin is given for <3 weeks or when tetracycline is given for <2 weeks [132, 133]. Until further data are forthcoming, it seems reasonable to treat bacterial infections such as those caused by *S. pneumoniae* until a patient is afebrile for 72 hours (C, III). Pneumonia caused by *M. pneumoniae* or *C. pneumoniae* should probably be treated for at least 2 weeks, as should Legionnaires' disease in immunocompetent individuals (B, II). Azithromycin may be used for shorter courses of treatment because of its longer half-life in tissue [133].

As cost considerations increase and hospital bed closures become commonplace, there is rising interest in the use of oral therapy whenever possible. For many pathogens, there is no clear advantage of intravenous therapy over oral therapy. However, for most patients admitted to the hospital, the common practice is at least to begin therapy with intravenous drugs.

There are no studies that verify superior outcomes when drugs are administered intravenously rather than orally (when the drugs are well absorbed). The Panel endorses use of oral antimicrobial agents for patients who tolerate these drugs if oral bioavailability and activity are adequate (A, III).

Changing from intravenous to oral therapy is associated with a number of economic, healthcare, and social benefits. This change reduces costs of treatment and shortens length of hospital stay. At least 13 randomized controlled trials have been conducted to address the issue of changing from parenteral to oral antibiotic treatment for a variety of infections including pneumonia. A review of these data [132] supports this change with the following provisos: a patient's condition should be improving clinically and the patient should be hemodynamically stable, able to ingest drugs, and have a functioning gastrointestinal tract (A, I). In most cases, these conditions are met within 3 days, and oral therapy can be given at that time. Ideally, the parenteral drug should be given in an oral formulation with adequate bioavailability; if no oral formulation is available, an oral agent with a similar spectrum of activity should be selected on the basis of in vitro or predicted susceptibility patterns of the established or probable pathogen.

Assessment of Response to Treatment

The expected response to treatment should be based on the clinical illness, pathogen, severity of illness, the host, and the chest radiographic findings. Subjective response is usually noted within 3–5 days of initiating treatment. Objective parameters include resolution of respiratory symptoms (cough or dyspnea), fever, the PO₂ level, the peripheral leukocyte count, and findings on serial radiographs. The most carefully documented response is time to defervescence. In young adults with pneumococcal pneumonia, the average duration of fever after treatment is 2.5 days; in patients with bacteremic pneumonia, it is 6–7 days; and in elderly patients, it also appears to be longer. Patients with mycoplasma pneumonia are usually afebrile within 1–2 days after treatment, and immunocompetent patients with Legionnaires' disease require an average of 5 days for defervescence.

In cases of bacteremic pneumonia, blood cultures usually become negative within 24–48 hours of treatment. The pathogen is usually suppressed in respiratory secretions within 24–48 hours as well; the major exception is *P. aeruginosa*, which may persist despite appropriate treatment, and *M. pneumoniae*, which usually persists despite effective therapy. Follow-up cultures of blood and sputum are not indicated for patients who respond to therapy, unless the pathogen is *M. tuberculosis*. The results of cultures of respiratory secretions from any source are likely to be deceptive after antimicrobial therapy; this concern especially applies to fastidious pathogens such as *S. pneumoniae* and *H. influenzae*, even for patients who fail to respond clinically [67].

Chest radiographic findings usually clear more slowly than do clinical findings, and multiple radiographs often represent unwarranted use of diagnostic resources for patients with pneumonia (A, II) [46]. During the first several days of treatment, there is often radiographic progression despite a good clinical response. Follow-up radiographs during hospitalization are indicated to assess the position of an endotracheal tube or a line and to exclude pneumothorax after central line placement and to determine reasons for failure to respond such as pneumothorax, progression of an infiltrate, cavitation, pulmonary edema, or ARDS. In terms of host factors, age and presence or absence of comorbid illness are important determinants of the rate of resolution. Radiographic findings for most patients with bacteremic pneumococcal pneumonia who are <50 years of age clear by 4 weeks; however, for older patients or those with underlying illnesses, particularly alcoholism or COPD, or those with extensive pneumonia on presentation, the rate of resolution slows considerably, and the radiographic findings for only 20%–30% may show clear by 4 weeks [135, 136]. *L. pneumophila* infection may take substantially longer to clear, with complete resolution in only 55% of cases by 12 weeks [134]. Follow-up radiographs to document resolution of infiltrates and to exclude underlying disease such as a neoplasm are advocated for selected patients who are >40 years of age and/or are smokers. The suggested time for follow-up radiographs is 7–12 weeks after initiation of treatment.

Patients Who Fail to Respond

In the event that there is either no response or deterioration in a patient's condition after initiation of empirical therapy, a number of possibilities should be considered (figure 3) (C, III).

1. Incorrect diagnosis:

Noninfectious illnesses that may account for the clinical and radiographic findings include congestive heart failure, pulmonary embolus, atelectasis, sarcoid, neoplasms, radiation pneumonitis, pulmonary drug reactions, BOOP, vasculitis, ARDS, pulmonary hemorrhage, and inflammatory lung disease.

2. Correct diagnosis:

If a correct diagnosis has been made but a patient fails to respond, the physician should consider each of the components of the HOST-DRUG-PATHOGEN triad.

a) *Host-related problem*—The overall reported mortality for hospitalized patients with CAP is 10%–15%; this figure includes patients with an established or likely etiologic diagnosis who are treated with appropriate antibiotics [8]. The mortality rate for patients with bacteremic pneumococcal pneumonia caused by penicillin-susceptible strains of *S. pneumoniae* who are treated with penicillin has been consistently reported at $\geq 20\%$ [84]. The usual explanation is that the treatment has been initiated too late or

that preexisting conditions preclude adequate response. Occasional patients have local lesions that preclude optimal response, such as an obstructing neoplasm or foreign body or a tooth that might have been aspirated. Empyema is an infrequent but important cause of failure to respond. Other complications include adverse drug reactions or other complications of medical management such as fluid overload, pulmonary superinfection, or line sepsis.

b) *Drug-related problem*—Whether or not a specific pathogen has been isolated, if a correct etiologic diagnosis of pneumonia has been made but a patient does not appear to be responding, the physician should always consider the possibility of a medication error. To do so includes assurance of use of the appropriate drug and appropriate dosing regimen as well as compliance. Access of the drug to the site of infection should be assured by excluding the presence of a sequestered focus of infection such as an empyema.

c) *Pathogen-related problem*—Alternative, additional, or unusual pathogens should be considered as well as the possibility that an infection is caused by a resistant pathogen. A wide variety of pathogens such as *M. tuberculosis*, fungi, viruses, nocardia, *C. psittaci*, hantavirus, *C. burnettii*, *P. carinii*, and multiresistant *S. pneumoniae* should be considered, depending on the status of a patient's defense mechanisms and on epidemiological factors.

Assessment of a Nonresponding Patient:

The assessment of a patient who fails to respond to initial empirical therapy should be based on the possibilities outlined above and in figure 3. Tests appropriate for individual disease entities should be performed to exclude noninfectious possibilities. Specific examples include ventilation perfusion lung scans, and in selected cases, pulmonary angiography to identify pulmonary emboli, P and C ANCA, and bronchoscopy, or in some cases open lung biopsy to diagnose a variety of noninfectious causes including neoplasms. Host factors that would influence the range of pathogens as well as response should be considered; examples are HIV infection, cystic fibrosis, neoplasms, recent travel, or exposures.

In cases in which infection is responsible for the clinical and radiographic findings, issues relating to the host-drug-pathogen triad should be taken into account for the workup. To rule out the presence of an endobronchial lesion or foreign body, bronchoscopy and/or CT may be of help. To ensure that a sequestered focus of infection such as a lung abscess or empyema has not developed, thereby preventing access of the drugs to the pathogens, obtaining a computed tomographic scan of the chest may be useful. When pleural effusions are detected on chest radiographs, ultrasonography can localize the collection and provide an estimate of the volume of fluid.

Infection caused by an unsuspected organism or a resistant pathogen must always be a concern as well in nonresponding patients. An aggressive attempt to obtain appropriate expectorated sputum samples may allow identification of such organisms on stain or culture, although the validity of such posttreatment specimens must be questioned because of the inability to culture *S. pneumoniae* and other fastidious pathogens and the frequent overgrowth by *S. aureus* and gram-negative bacilli. In selected cases, bronchoscopy may be necessary; the results of one study suggest that helpful information may be provided for up to 41%

of patients with CAP who fail to respond to initial empirical antimicrobial therapy [54].

Prevention of CAP

The annual impact of influenza is highly variable. During winters when influenza is epidemic, its impact on the frequency of CAP is sizable as a result both of primary influenza pneumonia and secondary bacterial pneumonia. Influenza vaccine is effective in limiting severe disease caused by influenza virus [114], and it is recommended that the vaccine be given annually to persons at increased risk for complications as well as to health care workers (A, I) [81].

Polyvalent vaccines of pneumococcal capsular polysaccharides have been shown to be effective in preventing pneumococcal pneumonia in American military recruits [137] and in young adult African males [138]. The currently available 23-valent vaccine has an aggregate efficacy of $\geq 60\%$ in preventing bacteremic pneumococcal infection in immunocompetent adults in the United States [139, 140]. Its efficacy tends to decline with age and may be negligible in immunocompromised hosts [141, 142]. It must be borne in mind that the pneumococcal vaccine consists of a mixture of antigens designed to prevent 23 immunologically distinct serotypes, the aggregate efficacy of which cannot equal that of a monovalent vaccine. Despite controversies over efficacy [142–144], the death rate associated with bacteremic pneumococcal infection among persons >64 years of age and/or with a variety of underlying systemic illnesses remains high. The Panel endorses current CDC guidelines for pneumococcal disease (B, II). More than half of patients hospitalized with pneumococcal disease have been hospitalized in the previous 5 years [145]. Consequently, unvaccinated patients with risk factors for pneumococcal disease and influenza should be vaccinated during hospitalization whenever possible (C, III). There is no contraindication for use of either pneumococcal or influenza vaccine immediately after an episode of pneumonia (i.e., before discharge from the hospital). The vaccines are inexpensive and can be given simultaneously.

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