GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Practice Guidelines for the Management of Community-Acquired Pneumonia in Adults

John G. Bartlett,[1] Scott F. Dowell,[2] Lionel A. Mandell,[6] Thomas M. File, Jr.,[3] Daniel M. Musher,[4] and Michael J. Fine[5]

[1]*Johns Hopkins University School of Medicine, Baltimore, Maryland,* [2]*Centers for Disease Control and Prevention, Atlanta, Georgia,* [3]*Northeastern Ohio Universities College of Medicine, Cleveland, Ohio,* [4]*Baylor College of Medicine and Veterans Affairs Medical Center, Houston, Texas, and* [5]*University of Pittsburgh, Pennsylvania, USA; and* [6]*McMaster University, Toronto, Canada*

Executive Summary

Guidelines for the management of community-acquired pneumonia were issued on behalf of the Infectious Diseases Society of America in April 1998. The present version represents a revision of these guidelines issued in February 2000; updates at 6- to 12-month intervals are anticipated. A summary of these guidelines follows.

Grading system. Recommendations are categorized by the letters A–D, according to the strength of the recommendation: A, good evidence to support the recommendation; B, moderate evidence to support the recommendation; C, poor evidence to support the recommendation; and D, evidence against the recommendation. The recommendations are also graded by the quality of the evidence to support the recommendation, on the basis of categories I–III; I, at least 1 randomized controlled trial supports the recommendation; II, evidence from at least 1 well-designed clinical trial without randomization supports the recommendation; and III, "expert opinion."

Chest radiography. Chest radiography is considered critical for establishing the diagnosis of pneumonia and for distinguishing this condition from acute bronchitis (AB), which is a common cause of antibiotic abuse.

Site of care. Recommendations regarding the decision for hospitalization are based on the methodology used in the clinical prediction rule for short-term mortality, from the publications of the Pneumonia Patient Outcome Research Team (Pneumonia PORT). Patients are stratified into 5 severity classes by means of a 2-step process. Class I indicates an age <50 years, with none of 5 comorbid conditions (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, or renal disease), normal or only mildly deranged vital signs, and normal mental status. In step 2, patients not assigned to risk class I are stratified in classes II–V on the basis of points assigned for 3 demographic variables (age, sex, and nursing home residency), 5 comorbid conditions (summarized above), 5 physical examination findings, and 7 laboratory and/or radiographic findings.

Patients in risk classes I and II do not usually require hospitalization, those in risk class III may require brief hospitalization, and those in risk classes IV and V usually require hospitalization. It should be noted that social factors, such as outpatient support mechanisms and probability of adherence, are not included in this assessment.

Laboratory tests. All patients thought to have pneumonia should undergo chest radiography. The following laboratory values should be determined for patients who are hospitalized: complete blood cell count and differential, serum creatinine, blood urea nitrogen, glucose, electrolytes, and liver function tests. HIV serology with informed consent should be considered, especially for persons aged 15–54 years. Oxygen saturation should be assessed. There should be 2 pretreatment blood cultures, as well as Gram staining and culture of expectorated sputum. Selected patients should have microbiological studies for tuberculosis and legionella infection. The preferred tests for detection of *Legionella* species are the urinary antigen assay for *Legionella pneumophila* serogroup 1 and culture with selective media. The rationale for performing microbiological studies to establish an etiologic diagnosis is based on attempts to improve care of the individual patient with pathogen-specific treatment; to improve care of other patients and to advance knowledge by detecting epidemiologically important organisms *(Legionella,* penicillin-resistant *Streptococcus pneumoniae,* and methicillin-resistant *Staphylococcus aureus);* to implement contact-tracing and antimicrobial prophylaxis in appropriate settings (such as cases of *Neisseria meningitidis* infection, *Haemophilus influenzae* type B infection, and tuberculosis); to prevent antibiotic abuse; and to reduce antibiotic expense.

Antimicrobial therapy. Recommendations are provided for pathogen-specific treatment in cases in which an etiologic diagnosis is established or strongly suspected. If this information

is not available initially but is subsequently reported, changing to the antimicrobial agent that is most cost-effective, least toxic, and most narrow in spectrum is encouraged. Recommendations for treating patients who require empirical antibiotic selection are based on severity of illness, pathogen probabilities, resistance patterns of *S. pneumoniae* (the most commonly implicated etiologic agent), and comorbid conditions.

The recommendation for outpatients is administration of a macrolide, doxycycline, or fluoroquinolone with enhanced activity against *S. pneumoniae.* For patients who are hospitalized, the recommendation is administration of a fluoroquinolone alone or an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) plus a macrolide. Patients hospitalized in the intensive care unit (ICU) should receive ceftriaxone, cefotaxime, ampicillin-sulbactam, or piperacillin-tazobactam in combination with a fluoroquinolone or macrolide. β-lactams, other than those noted, are not recommended. Intravenous antibiotics may be switched to oral agents when the patient is improving clinically, is hemodynamically stable, and is able to ingest drugs. Most patients show a clinical response within 3–5 days. Changes evident on chest radiographs usually lag behind the clinical response, and repeated chest radiography is generally not indicated for patients who respond. The failure to respond usually indicates an incorrect diagnosis; host failure; inappropriate antibiotic; inappropriate dose or route of administration; unusual or unanticipated pathogen; adverse drug reaction; or complication, such as pulmonary superinfection or empyema.

Prognosis. The most frequent causes of lethal community-acquired pneumonia are *S. pneumoniae* and *Legionella.* The most frequent reason for failure to respond is progression of pathophysiological changes, despite appropriate antibiotic treatment.

Pneumococcal pneumonia. *S. pneumoniae,* the most common identifiable etiologic agent of pneumonia in virtually all studies, accounts for about two-thirds of bacteremic pneumonia cases, and pneumococci are the most frequent cause of lethal community-acquired pneumonia. Management has been complicated in recent years by the evolution of multidrug resistance. β-lactams (amoxicillin, cefotaxime, and ceftriaxone) are generally regarded as the drugs of choice, although pneumonia caused by resistant strains (MIC, $\geqslant 2$ μg/mL) may not respond as readily as pneumonia caused by more susceptible strains. The activity of macrolides and doxycycline or other β-lactams, including cefuroxime, is good against penicillin-susceptible strains but less predictable with strains that show reduced penicillin-susceptibility. Vancomycin, linezolid, and quinupristin/dalfopristin are the only drugs with predictable in vitro activity. Fluoroquinolones are generally active against strains that are susceptible or resistant to penicillin, but recent reports indicate increasing resistance in selective locations that correlate with excessive fluoroquinolone use.

Prevention. The major preventive measures are use of influenza vaccine and use of pneumococcal vaccine, according to guidelines of the Advisory Council on Immunization Practices of the Centers for Disease Control and Prevention (CDC).

Performance indicators. Recommendations for performance indicators include the collection of blood culture specimens before antibiotic treatment and the institution of antibiotic treatment within 8 h of hospitalization, since both are supported on the basis of evidence-based trials. Additional performance indicators recommended are laboratory tests for *Legionella* in patients hospitalized in the ICU, demonstration of an infiltrate on chest radiographs of patients with an ICD-9 (International Classification of Diseases, 9th edition) code for pneumonia, and measurement of blood gases or pulse oximetry within 24 h of admission.

Introduction

Lower respiratory tract infections are the major cause of death in the world 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 (*Chlamydia pneumoniae* and hantavirus), new methods of microbial detection (PCR), and new antimicrobial agents (macrolides, β-lactam agents, fluoroquinolones, oxazolidinones, and streptogramins). Despite extensive studies, there are few conditions in medicine that are so controversial in terms of management. Guidelines for management were published in 1993 by the American Thoracic Society [1], the British Thoracic Society [2], and the Canadian Infectious Disease Society [3], as well as the Infectious Diseases Society of America (IDSA) in 1998 [4]. The present guidelines represent revised recommendations of the IDSA. Compared with previous guidelines, these guidelines are intended to reflect updated information, provide more extensive recommendations in selected areas, and indicate 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 (table 1). This is customary for quality standards from the IDSA [5]. 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 judgement.

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, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/

Table 1. Categories for ranking recommendations in the therapeutic guidelines.

Category	Description
Strength of recommendation	
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
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from at least 1 randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial without randomization
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

or localized rales), in a patient not hospitalized or residing in a long-term-care facility for ≥14 days before onset of symptoms. Symptoms of acute lower respiratory infection may include several (in most studies, at least 2) of the following: fever or hypothermia, rigors, sweats, new cough with or without sputum production or change in 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. From 1979 through 1994, the overall rates of death due to pneumonia and influenza increased by 59% (on the basis of ICD-9 codes on death certificates) in the United States [6]. Much of this increase is due to a greater proportion of persons aged ≥65 years; however, age-adjusted rates also increased by 22%, which suggests that other factors may have contributed to a changing epidemiology of pneumonia, including a greater proportion of the population with underlying medical conditions 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 [7, 8]. The incidence of CAP that requires hospitalization is estimated to be 258 persons per 100,000 population and 962 per 100,000 persons aged ≥65 years [8]. Although mortality has ranged from 2% to 30% among hospitalized patients in a variety of studies, the average is ~14% [9]. Mortality is estimated to be <1% for patients not hospitalized [9, 10]. The incidence of CAP is heavily weighted toward the winter months.

Prognosis, Risk Stratification, and the Initial Site-of-Treatment Decision

Knowledge about the prognosis of a disease allows physicians to inform their patients about the expected natural history of an illness, the likelihood of potential complications, and the probability of successful treatment. Understanding the prognosis of CAP is of particular clinical relevance, since it ranges from rapid recovery from symptoms without functional impairment to serious morbid complications and death. The ability to accurately predict medical outcomes in cases of CAP has a major impact on management. The decision to hospitalize a patient or to treat him or her as an outpatient (figure 1) is perhaps the single most important clinical decision made by physicians during the entire course of illness, which has direct bearing on the location and intensity of laboratory evaluation, antibiotic therapy, and costs. The estimated total treatment cost for an episode of CAP managed in the hospital is $7500 (US dollars) [11], >20-fold higher than the cost of outpatient treatment.

Numerous studies have identified risk factors for death in cases of CAP [9, 10, 12]. These factors were well-defined in the pre–penicillin era; studies of adults showed an increased risk with alcohol consumption, increasing age, the presence of leukopenia, the presence of bacteremia, and radiographic changes [12]. More recent studies have confirmed these findings [2, 13–18]. Independent associations with increased mortality have also been demonstrated for a variety of comorbid illnesses, such as active malignancies [10, 16, 19], immunosuppression [20, 21], neurological disease [19, 22, 23], congestive heart failure [10, 17, 19], coronary artery disease [19], and diabetes mellitus [10, 19, 24]. Signs and symptoms independently associated with increased mortality consist of dyspnea [10], chills [25], altered mental status [10, 19, 23, 26], hypothermia or hyperthermia [10, 16, 17, 20], tachypnea [10, 19, 23, 27], and hypotension (diastolic and systolic) [10, 19, 26–28].

Laboratory and radiographic findings independently associated with increased mortality are hyponatremia [10, 19], hyperglycemia [10, 19], azotemia [10, 19, 27, 28], hypoalbuminemia [16, 19, 22, 25], hypoxemia [10, 19], liver function test abnormalities [19], and pleural effusion [29]. Infections due to gram-negative bacilli or *S. aureus,* postobstructive pneumonia, and aspiration pneumonia are also independently associated with higher mortality [30].

Despite our knowledge regarding the associations of clinical, laboratory, and radiographic factors and patient mortality, there is wide geographic variation in hospital admission rates for CAP [31, 32]. This variation suggests that physicians do not use a uniform strategy to relate the decision to hospitalize to the prognosis. In fact, physicians often overestimate the risk of death for patients with CAP, and the degree of overesti-
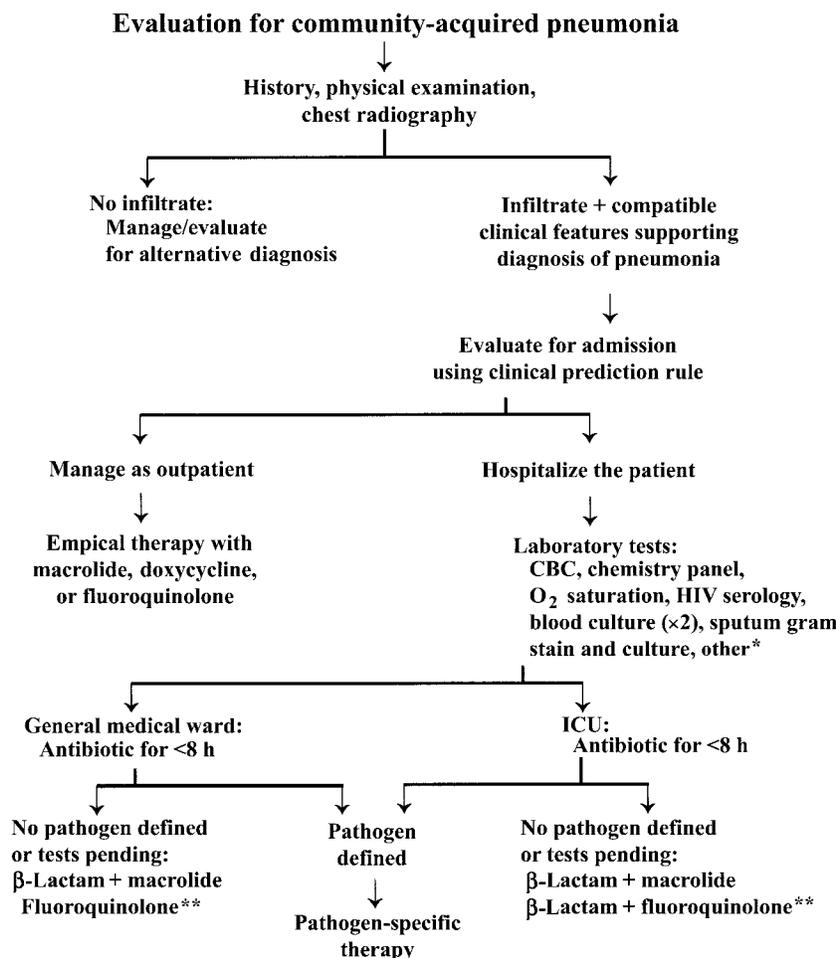
Evaluation for community-acquired pneumonia
↓
History, physical examination, chest radiography

No infiltrate: Manage/evaluate for alternative diagnosis

Infiltrate + compatible clinical features supporting diagnosis of pneumonia
↓
Evaluate for admission using clinical prediction rule

Manage as outpatient
↓
Empical therapy with macrolide, doxycycline, or fluoroquinolone

Hospitalize the patient
↓
Laboratory tests: CBC, chemistry panel, O₂ saturation, HIV serology, blood culture (×2), sputum gram stain and culture, other*

General medical ward: Antibiotic for <8 h

No pathogen defined or tests pending: β-Lactam + macrolide Fluoroquinolone**

Pathogen defined
↓
Pathogen-specific therapy

ICU: Antibiotic for <8 h

No pathogen defined or tests pending: β-Lactam + macrolide β-Lactam + fluoroquinolone**

Figure 1. Evaluation for diagnosis and management of community-acquired pneumonia, including site, duration, and type of treatment. β-Lactam: cefotaxime, ceftriaxone, or a β-lactam/β-lactamase inhibitor. Fluoroquinolone: levofloxacin, moxifloxacin, or gatifloxacin or another fluoroquinolone with enhanced antipneumococcal activity. Macrolide: erythromycin, clarithromycin, or azithromycin. CBC, complete blood cell count; ICU, intensive care unit. *Other tests for selected patients: see text, Diagnostic Evaluation: Etiology. **See table 15 for special considerations.

mation is independently associated with the decision to hospitalize [30].

Over the past 10 years, at least 13 studies have used multivariate analysis to identify predictors of prognosis for patients with CAP [10, 16–20, 25–27, 33–35]. The Pneumonia PORT developed a methodologically sound clinical prediction rule that quantifies short-term mortality for patients with this illness [10]. Used as a guideline, this rule may help physicians make decisions about the initial location and intensity of treatment for patients with this illness (table 2).

The Pneumonia PORT prediction rule was derived with 14,199 inpatients with CAP; it was independently validated with 38,039 inpatients with CAP and 2287 inpatients and outpatients prospectively enrolled in the Pneumonia PORT cohort study. With this rule, patients are stratified into 5 severity classes by means of a 2-step process. In step 1, patients are classified as risk class I (the lowest severity level) if they are aged ≤50 years,

have none of 5 important comorbid conditions (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, or renal disease), and have normal or only mildly deranged vital signs and normal mental status. In step 2, all patients who are not assigned to risk class I on the basis of the initial history and physical examination findings alone are stratified into classes II–V, on the basis of points assigned for 3 demographic variables (age, sex, and nursing home residence), 5 comorbid conditions (listed above), 5 physical examination findings (altered mental status, tachypnea, tachycardia, systolic hypotension, hypothermia, or hyperthermia), and 7 laboratory or radiographic findings (acidemia, elevated blood urea nitrogen, hyponatremia, hyperglycemia, anemia, hypoxemia, or pleural effusion; table 3). Point assignments correspond with the following classes: ≤70, class II; 71–90, class III; 91–130, class IV; and >130, class V.

In the derivation and validation of this rule, mortality was

Table 2. Comparison of risk class–specific mortality rates in the derivation and validation cohorts.

Risk class[a] (total points)	MedisGroups derivation cohort		MedisGroups validation cohort		Pneumonia PORT validation cohort					
					Inpatients		Outpatients		All patients	
	n	Mortality, %	n	Mortality, %	n	Mortality, %	n	Mortality, %	n	Mortality, %
I	1372	0.4	3034	0.1	185	0.5	587	0.0	772	0.1
II (≤70)	2412	0.7	5778	0.6	233	0.9	244	0.4	477	0.6
III (71–90)	2632	2.8	6790	2.8	254	1.2	72	0.0	326	0.9
IV (91–130)	4697	8.5	13,104	8.2	446	9.0	40	12.5	486	9.3
V (>130)	3086	31.1	9333	29.2	225	27.1	1	0.0	226	27.0
Total	14,199	10.2	38,039	10.6	1343	8.0	944	0.6	2287	5.2

NOTE.   No statistically significant differences in overall mortality or mortality within risk class existed among patients in the MedisGroups derivation, MedisGroups validation, and overall Pneumonia Patient Outcome Research Team (PORT) validation cohorts (*n* denotes the no. of patients within each risk class in the derivation and validation cohorts). *P* values for the comparisons of mortality across risk classes are as follows: class I, *P* = .22; class II, *P* = .67; class III, *P* = .12; class IV, *P* = .69; and class V, *P* = .09.

[a] Risk class I was determined by the absence of all predictors identified in step 1 of the prediction rule. Risk classes II–V were determined by a patient's total risk score, which is computed by use of the point scoring system shown in table 3.

low for risk classes I–III (0.1%–2.8%), intermediate for class IV (8.2%–9.3%), and high for class V (27.0%–31.1%). Increases in risk class were also associated with subsequent hospitalization and delayed return to usual activities for outpatients and with rates of admission to the ICU and length of stay for inpatients in the Pneumonia PORT validation cohort. On the basis of these observations, Pneumonia PORT investigators suggest that patients in risk classes I or II generally are candidates for outpatient treatment, risk class III patients are potential candidates for outpatient treatment or brief inpatient observation, and patients in classes IV and V should be hospitalized (table 4). Estimates from the Pneumonia PORT cohort study suggest that these recommendations would reduce the proportion of patients receiving traditional inpatient care by 31% and that there would be a brief observational inpatient stay for an additional 19%.

The effectiveness and safety of applying the Pneumonia PORT prediction rule to the initial site of care for an independent population of patients with CAP have been examined with use of a modified version of the Pneumonia PORT prediction rule [36]. Emergency room physicians were educated about the rule and were encouraged to treat those in risk classes I–III as outpatients, with close, structured follow-up and provision of oral clarithromycin at no cost to the patient, if desired. The outcomes for those treated at home during this intervention phase were compared with the outcomes for historical control subjects from the time period immediately preceding the intervention.

During the intervention period, there were 166 eligible patients classified as "low risk" for short-term mortality (risk classes I–III) for comparison with 147 control subjects. The percentage treated initially as outpatients was higher during the intervention period than during the control period (57% vs. 42%; relative increase of 36%; *P* = .01). When initial plus subsequent hospitalization was used as the outcome measure, there was a trend toward more outpatient care during the intervention period, but the difference was no longer statistically significant (52% vs. 42%; *P* = .07). None of those initially treated

in the outpatient setting during the intervention period died within 4 weeks of presentation.

A second multicenter controlled trial subsequently assessed the effectiveness and safety of using the Pneumonia PORT prediction rule for the initial site-of-treatment decision [37]. In this trial, 19 emergency departments were randomly assigned either to continue conventional management of CAP or to implement a critical pathway that included the Pneumonia PORT prediction rule to guide the admission decision. Emergency room physicians were educated about the rule and were encouraged to treat those in risk classes I–III as outpatients with oral levofloxacin. Overall, 1743 patients with CAP were enrolled in this 6-month study. Use of the prediction rule resulted in an 18% reduction in the admission of low-risk patients (31% vs. 49%; *P* = .013). Use of the rule did not result in an increase in mortality or morbidity and did not compromise patients' 30-day functional status. These studies support use of the Pneumonia PORT prediction rule to help physicians identify low-risk patients who can be safely treated in the outpatient setting.

The IDSA panel endorses the findings of the Pneumonia PORT prediction rule, which identifies valid predictors for mortality and provides a rational foundation for the decision regarding hospitalization. However, it should be emphasized that the PORT prediction rule is validated as a mortality prediction model and not as a method to triage patients with CAP. New studies are required to test the basic premise underlying the use of this rule in the initial site-of-treatment decision, so that patients classified as "low risk" and treated in the outpatient setting will have outcomes equivalent to or better than those of similar "low-risk" patients who are hospitalized.

It is important to note that prediction rules are meant to contribute to rather than to supersede physicians' judgment. Another limitation is that factors other than severity of illness must also be considered in determining whether an individual patient is a candidate for outpatient care. Patients designated as "low risk" may have important medical and psychosocial contraindications to outpatient care, including expected compliance problems with medical treatment or poor social support

Table 3. Scoring system for step 2 of the prediction rule: assignment to risk classes II–V.

Patient characteristic	Points assigned[a]
Demographic factor	
Age	
Male	No. of years of age
Female	No. of years of age − 10
Nursing home resident	+10
Comorbid illnesses	
Neoplastic disease[b]	+30
Liver disease[c]	+20
Congestive heart failure[d]	+10
Cerebrovascular disease[e]	+10
Renal disease[f]	+10
Physical examination finding	
Altered mental status[g]	+20
Respiratory rate >30 breaths/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or >40°C	+15
Pulse >125 beats/min	+10
Laboratory or radiographic finding	
Arterial pH <7.35	+30
Blood urea nitrogen >30 mg/dL	+20
Sodium <130 mEq/L	+20
Glucose >250 mg/dL	+10
Hematocrit <30%	+10
Arterial partial pressure of oxygen <60 mm Hg[h]	+10
Pleural effusion	+10

[a] A total point score for a given patient is obtained by adding the patient's age in years (age −10, for females) and the points for each applicable patient characteristic. Points assigned to each predictor variable were based on coefficients obtained from the logistic regression model used in step 2 of the prediction rule.

[b] Any cancer except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within 1 year of presentation.

[c] A clinical or histologic diagnosis of cirrhosis or other form of chronic liver disease such as chronic active hepatitis.

[d] Systolic or diastolic ventricular dysfunction documented by history and physical examination, as well as chest radiography, echocardiography, Muga scanning, or left ventriculography.

[e] A clinical diagnosis of stroke, transient ischemic attack, or stroke documented by MRI or computed axial tomography.

[f] A history of chronic renal disease or abnormal blood urea nitrogen and creatinine values documented in the medical record.

[g] Disorientation (to person, place, or time, not known to be chronic), stupor, or coma.

[h] In the Pneumonia Patient Outcome Research Team cohort study, an oxygen saturation value <90% on pulse oximetry or intubation before admission was also considered abnormal.

at home. Ability to maintain oral intake, history of substance abuse, cognitive impairment, and ability to perform activities of daily living must be considered. In addition, patients may have rare conditions, such as severe neuromuscular disease or immunosuppression, which are not included as predictors in these prediction rules but increase the likelihood of a poor prognosis.

Prediction rules may also oversimplify the way physicians interpret important predictor variables. For example, extreme alterations in any one variable have the same effect on risk stratification as lesser changes, despite obvious differences in clinical import (e.g., a systolic blood pressure of 40 mm Hg vs. one of 88 mm Hg). Furthermore, such rules discount the cumulative importance of multiple simultaneous physiological derangements, especially if each derangement alone does not reach the threshold that defines an abnormal value (e.g., systolic

blood pressure of 90/40 mm Hg, respiratory rate of 28 breaths/min, and pulse of 120 beats/min). Finally, prediction rules often neglect the importance of patients' preferences in clinical decision-making. This point is highlighted by the observation that the vast majority of low-risk patients with CAP do not have their preferences for site of care solicited, despite strong preferences for outpatient care [38].

Role of Specific Pathogens in CAP

Prospective studies evaluating the causes of CAP in adults have failed to identify the cause of 40%–60% of cases of CAP and have detected ≥2 etiologies in 2%–5% [2, 7, 26, 39, 40]. The most common etiologic agent identified in virtually all studies of CAP is *S. pneumoniae,* which accounts for about two-thirds of all cases of bacteremic pneumonia cases [9]. Other pathogens implicated less frequently include *H. influenzae* (most strains of which are nontypeable), *Mycoplasma pneumoniae, C. pneumoniae, S. aureus, Streptococcus pyogenes, N. meningitidis, Moraxella catarrhalis, Klebsiella pneumoniae* and other gram-negative rods, *Legionella* species, influenza virus (depending on the season), respiratory syncytial virus, adenovirus, parainfluenza virus, and other microbes. The frequency of other etiologies is dependent on specific epidemiological factors, as with *Chlamydia psittaci* (psittacosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), and endemic fungi (histoplasmosis, blastomycosis, and coccidioidomycosis).

Comparisons of relative frequency of each of the etiologies of pneumonia are hampered by the varying levels of sensitivity and specificity of the tests used for each of the pathogens that they detect; for example, in some studies, tests used for legionella infections provide a much higher degree of sensitivity and possibly specificity than do tests used for pneumococcal 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 [39]. Even time-honored beliefs, such

Table 4. Risk-class mortality rates.

Risk class	No. of points	Validation cohort		Recommended site of care
		No. of patients	Mortality, %	
I	—[a]	3034	0.1	Outpatient
II	≤70	5778	0.6	Outpatient
III	71–90	6790	2.8	Outpatient or brief inpatient
IV	91–130	13,104	8.2	Inpatient
V	>130	9333	29.2	Inpatient

NOTE. Table is adapted from [10].
[a] Absence of predictors.

Table 5.   Diagnostic studies for evaluation of community-acquired pneumonia.

Baseline assessment
    Chest radiography to substantiate diagnosis of pneumonia, to detect associated lung diseases, to gain insight
        into causative agent (in some cases), to assess severity, and as baseline to assess response
Outpatients
    Sputum Gram stain and culture for conventional bacteria are optional
Inpatients
    Determination of complete blood cell and differential counts
        Serum creatinine, urea nitrogen, glucose, electrolyte, bilirubin, and liver enzyme values
        HIV serological status for persons aged 15–54 years
        O_2 saturation arterial blood gas values for selected patients
    Blood cultures ($\times$2; before treatment)
    Gram stain and culture of sputum[a]
    Test for *Mycobacterium tuberculosis,* with acid-fast bacilli staining and culture for selected patients, especially
        those with cough for >1 mo, other common symptoms, or suggestive radiographic changes
    Test for *Legionella* in selected patients, including all seriously ill patients without an alternative diagnosis, es-
        pecially if aged >40 years, immunocompromised, or nonresponsive to β-lactam antibiotics, if clinical
        features are suggestive of this diagnosis, or in outbreak settings
    Thoracentesis with stain, culture, and determination of pH and leukocyte count differential (pleural fluid)
    Alternative specimens to expectorated sputum
        Aspirates of intubated patients, tracheostomy aspirates, and nasotracheal aspirates: manage as with expec-
        torated sputum
        Induced sputum: recommended for detection of *M. tuberculosis* or *Pneumocystis carinii*
        Bronchoscopy (see text under Special Considerations: Pnemococcal Pneumonia)
        Transtracheal aspiration: recommended only in cases of enigmatic pneumonia, to be done by persons
        skilled in the technique, preferably before antibiotic treatment
Optional
    Additional cytological or microbiological tests, as listed in table 8, depending on clinical features, available
        resources, underlying conditions, and/or epidemiological associations of the patient
    Serum: to be frozen and saved for serological analysis, if needed[b]

    [a] Should be deep-cough specimen obtained before antibiotic therapy. Gram stain should be interpreted by trained personnel and culture 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 infection with these. For hospitalized patients with severe pneumonia or clinical features that suggest legionnaires' disease, perform culture and urinary antigen testing for *Legionella.* Inability to obtain specimens for diagnostic studies should not delay antibiotic treatment of acutely ill patients.
    [b] Serological tests would include those for *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae,* or others (i.e., viruses, *Chlamydia psittaci,* or *Coxiella burnetii*), depending on the circumstances.

as the absence of productive cough or inflammatory sputum in pneumonia due to *Mycoplasma, Legionella,* or *Chlamydia* species, have not withstood close inspection. On the other hand, most comparisons have involved relatively small numbers of patients and have not evaluated the potential for separating causes by use of constellations of symptoms and physical findings.

In one study, as yet unconfirmed, that compared patients identified in a prospective standardized fashion, a scoring system using 5 symptoms and laboratory abnormalities was able to differentiate most patients with legionnaires' disease from the other patients [41]. A similar type of system has been devised for identifying patients with hantavirus pulmonary syndrome (HPS) [42]. If validated, such scoring systems may be useful for identifying patients who should undergo specific diagnostic tests (which are too expensive to use routinely for all patients with CAP) and be empirically treated with specific antimicrobial drugs while test results are pending.

Certain pathogens cause pneumonia more commonly among persons with specific risk factors. For instance, pneumococcal pneumonia is especially likely to occur in the elderly and in patients with a variety of medical conditions, including alcoholism, chronic cardiovascular disease, chronic obstructed airway disease, immunoglobulin deficiency, hematologic malig-

nancy, and HIV infection. However, outbreaks occur among young adults under conditions of crowding, such as in army camps or prisons. *S. pneumoniae* is second only to *Pneumocystis carinii* as the most common identifiable cause of acute pneumonia in patients with AIDS [43–45]. *Legionella* is an opportunistic pathogen; legionella pneumonia is rarely recognized in 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, smokers, and possibly those with AIDS [46]. Although *M. pneumoniae* historically has been thought primarily to involve children and young adults, some evidence suggests that it causes pneumonia in healthy adults of any age [8].

There are seasonal differences in incidence of many of the causes of CAP. Pneumonia due to *S. pneumoniae, H. influenzae,* and influenza occurs predominantly in winter months, whereas *C. pneumoniae* appears to cause pneumonia year-round. Although there is a summer prevalence of outbreaks of legionnaires' disease, sporadic cases occur with similar frequency during all seasons [8, 46]. Some studies suggest that there is no seasonal variation in mycoplasma infection; however, other data suggest that its incidence is greatest during the fall and winter months [47].

Table 6. Rationale for establishing an etiologic diagnosis.

Improve care of the individual patient
  To permit optimal antibiotic selection specifically directed at the causative agent
  To allow for a rational basis for change from parenteral to oral therapy and for a change in therapy necessitated by an adverse drug reaction
  To permit antibiotic selection that limits the consequences of injudicious antibiotic use in terms of cost to the patient, inducible resistance (e.g., inducible β-lactamases), and adverse drug reactions
Improve care of other patients and advance knowledge
  To identify pathogens of potential epidemiological significance, such as *Legionella,* hantavirus, and penicillin-resistant *Streptococcus pneumoniae*
  To identify newly emergent pathogens (hantavirus)
  To identify drug-resistant pathogens and monitor trends (drug-resistant *S. pneumoniae,* β-lactamase–producing *Haemophilus influenzae,* or methicillin-resistant *Staphylococcus aureus*)
  To prompt contact-tracing and antimicrobial prophylaxis *(Neisseria meningitidis, H. influenzae* type b, *Mycobacterium tuberculosis)*
  To permit antibiotic selection that limits the effects of antibiotic overuse on the community
Doing so is cost efficient
  Average cost of standard microbiological studies is <1% of the average hospital bill
  Narrow-spectrum agents may be less expensive
  Although many reports indicate that the yield of pathogens in expectorated sputum from patients with CAP is only 30%–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 choice), and a specimen of good quality that does not show or yield *S. 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, because conventional cultures of posttreatment specimens are relatively useless

There are other temporal variations in 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 incidence of mycoplasma infections occur every 3–6 years [47, 48]. Year-to-year variations may also occur with pneumococcal pneumonia [49].

Little is known about geographic differences in the incidence of pneumonia. Surveillance data from the CDC suggest that legionnaires' disease occurs with highest incidence in northeastern states and states in the Great Lakes area [46]; however, differences in ascertainment of disease may be a contributing factor. The incidence of pneumonia due to pathogens that are environmentally related would be expected to vary 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 (which can spread contaminated water via aerosol droplets), ideal meteorological conditions for transporting aerosols to susceptible hosts, and presence of susceptible hosts. Alterations in any of these variables would probably 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 HPS in the southwestern United States in 1993 [50].

Diagnostic Evaluation

Pneumonia should be suspected in patients with newly acquired lower respiratory symptoms (cough, sputum production, and/or dyspnea), especially if accompanied by fever, altered breath sounds, and rales. It is recognized that there must be a balance between reasonable diagnostic testing (table 5) and empirical therapy. The importance of establishing the diagnosis of pneumonia and its cause is heightened with the increasing concern about antibiotic overuse.

Chest Radiography

The diagnosis of CAP is based on a combination of clinical and laboratory (including microbiological) data. The differential diagnosis of lower respiratory symptoms is extensive and includes upper and lower respiratory tract infections, as well as noninfectious causes (e.g., reactive airways disease, atelectasis, congestive heart failure, bronchiolitis obliterans with organizing pneumonia [BOOP], vasculitis, pulmonary embolism, and pulmonary malignancy). Most cases of upper respiratory tract infection and AB are of viral origin, do not require antimicrobial therapy, and are the source of great antibiotic abuse [51, 52]. By contrast, antimicrobial therapy is usually indicated for pneumonia, and a chest radiography is usually necessary to establish the diagnosis of pneumonia. Physical examination to detect rales or bronchial breath sounds is neither sensitive nor specific for detecting pneumonia [53]. Chest radiography is considered sensitive and, occasionally, is useful for determining the etiologic diagnosis, the prognosis, and alternative diagnoses or associated conditions.

Chest radiographs in patients with *P. carinii* pneumonia (PCP) are false-negative for up to 30% of patients, but this exception is not relevant for the immunocompetent adult host [54]. One study showed spiral CT scans are significantly more sensitive in detecting pulmonary infiltrates [55], but the clinical significance of these results is unclear, and the IDSA panel does

Table 7. Epidemiological conditions related to specific pathogens in patients with selected community-acquired pneumonia.

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae* and anaerobes
COPD and/or smoking	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Legionella* species
Nursing home residency	*S. pneumoniae,* gram-negative bacilli, *H. influenzae, Staphylococcus aureus,* anaerobes, and *Chlamydia pneumoniae*
Poor dental hygiene	Anaerobes
Epidemic legionnaires' disease	*Legionella* species
Exposure to bats or soil enriched with bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
HIV infection (early stage)	*S. pneumoniae, H. influenzae,* and *Mycobacterium tuberculosis*
HIV infection (late stage)	Above plus *P. carinii, Cryptococcus,* and *Histoplasma* species
Travel to southwestern US	*Coccidioides* species
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Influenza active in community	Influenza, *S. pneumoniae, S. aureus, Streptococcus pyogenes,* and *H. influenzae*
Suspected large-volume aspiration	Anaerobes (chemical pneumonitis, obstruction)
Structural disease of lung (bronchiectasis, cystic fibrosis, etc.)	*Pseudonomas aeruginosa, Burkholderia (Pseudomonas) cepacia,* and *S. aureus*
Injection drug use	*S. aureus,* anaerobes, *M. tuberculosis,* and *S. pneumoniae*
Airway obstruction	Anaerobes, *S. pneumoniae, H. influenzae,* and *S. aureus*

NOTE.   COPD, chronic obstructive pulmonary disease.

not endorse the routine use of this technology because of the preliminary nature of the data and high cost of the procedure.

At times of limited resources, it may seem attractive to treat patients for CAP on the basis of presenting manifestations, without radiographic confirmation. 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 that suggest pneumonitis ranges from only 3% in a general outpatient setting to 28% in an emergency department [56, 57]. The IDSA panel recommends that chest radiography be included in the routine evaluation of patients for whom pneumonia is considered a likely diagnosis (A-II).

Etiology

The emphasis on microbiological studies (Gram staining and culture of expectorated sputum) in the IDSA guidelines represents a difference from the guidelines of the American Thoracic Society [1]. Arguments against microbiological studies include the low yield in many reports and the lack of documented benefit in terms of cost or outcome. A concern of the IDSA panel members is our perception that the quality of microbiological technology, as applied to respiratory secretions, has deteriorated substantially, compared with that in an earlier era [12]. Furthermore, it is our perception that regulations of the Clinical Laboratory Improvement Act, which discourage physicians from examining sputum samples microscopically, contributed to this decline. Although no data clearly demonstrate the cost-effectiveness or other advantages of attempts to identify pathogens, studies specifically designed to address this issue have not been reported.

Our rationale for the preservation of microbiological and immunologic testing is summarized in table 6, which classifies advantages with regard to the individual patient, society, and costs. The desire to identify the etiologic agent is heightened by concern about empirical selection of drugs, because of the increasing microbial resistance, unnecessary costs, and avoidable side effects. In addition, the work of prior investigators and their microbiological findings provide the rationale considered essential to the creation of guidelines based on probable etiologic agents.

A detailed history may be helpful for suggesting a diagnosis. Epidemiological clues that may lead to diagnostic considerations are listed in table 7. Certain findings have historically been identified as clues to specific causes of pneumonia, although these have not been confined to controlled studies. Acute onset, a single episode of shaking with chills (rigor), and pleurisy suggest pneumococcal infection. Prodromal fever and myalgia followed by pulmonary edema and hypotension are characteristic of HPS. Underlying COPD is more often seen with pneumonia due to *H. influenzae* or *M. catarrhalis,* separately or together with *S. pneumoniae.* Putrid sputum indicates infection caused by anaerobic bacteria. Although many studies of CAP have found that clinical features often do not distinguish etiologic agents [39, 58, 59], others support the utility of clinical clues for supporting an etiologic diagnosis [41, 60].

Once the clinical diagnosis of CAP has been made, consideration should be given to microbiological diagnosis with bacteriologic studies of sputum and blood [61–66]. Practice standards for collection, transport, and processing of respiratory secretions to detect common bacterial pathogens are summarized in table 8. Many pathogens require specialized tests for their detection, which are summarized in table 9. The rapid

Table 8. Recommendations for expectorated sputum collection, transport, and processing.

Specimen should be obtained by deep cough and have gross purulence; it should be obtained before treatment with antimicrobial agents and in the presence of a health care provider

Specimen should be immediately transported to the laboratory for prompt processing

A purulent portion is selected for Gram staining and culture; Quellung staining should be done when available

Cytological screening should be done under low-power magnification (×100) to determine the cellular composition (see text, Diagnostic Evaluation: Etiology); cytological assessment is not necessary for screening specimens for detection of respiratory viruses, *Legionella* species, or mycobacteria

Culture should be performed with use of standard techniques and results reported with semiquantitative assessment; most pathogens are recovered in 3–4+ growth, indicating >5 colonies, in the second quadrant.

diagnostic test for routine use is Gram staining of respiratory secretions, usually expectorated sputum; others include direct fluorescent antibody (DFA) staining of sputum or urinary antigen assay for *Legionella,* for use in selected cases, urinary antigen assay for *S. pneumoniae,* acid-fast bacilli (AFB) staining for detection of mycobacterial infections, and several tests for influenza.

Many rapid diagnostic tests, such as PCR, are in early development, not commonly available, or not sufficiently reliable [66]. PCR testing for detection of *Mycobacterium tuberculosis* is the only PCR test for detection of a respiratory tract pathogen that has been cleared by the US Food and Drug Administration (FDA), but it is recommended for use only with specimens that contain AFB on direct smears. Diagnostic procedures that provide identification of a specific etiology within 24–72 h can still be useful for guiding continued therapy.

The etiologic diagnosis can be useful for both prognostic and therapeutic purposes. Once a diagnosis has been established, the failure to respond to treatment can be dealt with in a logical fashion based on the causative organism and its documented antibiotic susceptibility, rather than by empiric selection of antimicrobial agents with a broader or different spectrum. Furthermore, if a drug reaction develops, an appropriate substitute can be readily selected.

Performance of blood cultures within 24 h of admission for CAP is associated with a significant reduction in 30-day mortality [67]. With regard to sputum bacteriology, several studies have suggested that mortality associated with CAP in hospitalized patients is the same for those with and without an etiologic diagnosis [68–70]. These studies were not specifically designed to test the hypothesis. Instead, the conclusion is based on retrospective analyses of cases with and without an etiologic diagnosis. Other outcomes also of interest that have not been assessed are length of stay, cost, resource use, and morbidity.

Some studies, although uncontrolled, do suggest benefit of these diagnostic studies [71–76]. For example, Boerner and Zwadyk [64] reported that a positive early diagnosis by sputum Gram staining correlated with more rapid resolution of fever after initiation of antimicrobial therapy. An additional study

by Torres et al. [76] showed that inadequate antibiotic treatment was clearly related to poor outcomes, which suggests that the establishment of an etiologic diagnosis is important.

The frequency of microbiological studies for CAP patients is highly variable. A report from the Pneumonia PORT study, with analysis of 1343 hospitalized patients during 1991–1994, showed that the frequencies of sputum Gram staining and sputum culture within 48 h of admission were 53% and 58%, respectively [77]. These studies were done on only 8%–11% of 944 outpatients with CAP. Participating centers in this and most other published studies of CAP are academic institutions at which microbiological studies are probably more frequent than in other health care settings. The finding of a likely pathogen in blood cultures averages 11% in published reports concerning hospitalized patients with CAP [9]. The yield with sputum studies is highly variable, ranging from 29% to 90% for hospitalized patients and usually <20% for outpatients [2, 26, 28, 36, 41, 67, 75–77]. The large variation among studies is presumably explained by variations in the quality of microbiological analyses, epidemiological patterns, and the patient population served.

It is our consensus that establishment of an etiologic diagnosis, with performance of blood cultures before initiation of antimicrobial treatment (A-I) and sputum Gram staining and culture (B-II), has value for patients who require hospitalization. The goal is to establish a specific diagnosis that can be used 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 these cases.

Etiologic diagnosis. Confidence in the accuracy of the diagnosis depends on the pathogen and on the diagnostic test, as follows.

1. Diagnosis definite: a definite etiology is established by a compatible clinical syndrome plus the recovery of a probable etiologic agent from an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate) or the 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 10) (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. Diagnosis probable: a probable etiologic diagnosis is established by a compatible clinical syndrome with detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, bronchoscopic aspirate, or quantitatively cultured bronchoscopic bronchoalveolar lavage [BAL] fluid or brush catheter specimen). With semiquantitative culture, the pathogen should be recovered in moderate to heavy growth (B-II).

Tests or specimens used for etiologic diagnosis. The following tests or types of specimens are used to establish an etiologic diagnosis.

1. Body fluids: blood culture specimens (with ≥2 needlesticks performed at separate sites) should be obtained from patients who require hospitalization for acute pneumonia (A-I). Potentially infected body fluids from other anatomic sites, including pleural fluid, joint fluid, and CSF, should have Gram staining and culture if warranted by the clinical presentation.

2. Sputum examination (table 8 and figure 2): the value of Gram staining of expectorated sputum is debated [60, 62, 63, 68–70, 75–80], but we recommend this relatively simple, inexpensive procedure for guiding initial selection of antimicrobial therapy, provided that a deep-cough specimen is obtained before antibiotic therapy, rapidly transported, and properly processed in the laboratory within a few hours of collection (B-II). Therapy with antimicrobial agents should not be delayed for acutely ill patients because of the 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 judging the acceptability of specimens include the relative number of polymorphonuclear cells (PMN) and squamous epithelial cells (SEC) in patients with normal or elevated WBC counts, determined with use of a low-power-field examination (LPF); the acceptable values range from >25 PMN+ < 10 SEC/LPF to <25 SEC/LPF, based on correlation of culture results with clinical findings and results of transtracheal aspiration (A-I) [81, 82]. Some authorities recommend a criterion of >10 WBC per SEC. *Mycobacteria* and *Legionella* species are exceptions, since microscopic criteria may yield misleading results.

Cultures should be performed rapidly [83], although the consequence of time delays in processing is disputed [84]. Interpretations of expectorated sputum cultures should include clinical correlations and semiquantitative results. In office practice, it may not be realistic to perform Gram staining in a timely manner to guide antibiotic decisions, but a slide may be prepared, air-dried, and heat-fixed for subsequent interpretation (C-III).

Numerous studies support the use of routine microscopic examination of a gram-stained sputum sample, with recognition of lancet-shaped gram-positive diplococci that suggest *S. pneumoniae.* Most show the sensitivity of sputum Gram staining for patients with pneumococcal pneumonia to be 50%–60% and the specificity to be >80% [60, 63–65, 75]. In a prospective study of 144 patients admitted to the hospital with CAP, 59 (41%) had a valid specimen obtained, with the cytological criteria of >25 PMN and <10 SEC evident on low-power magnification. The gram-stained smears of 47 valid specimens by these criteria showed a predominant bacterial morphotype that predicted the blood culture isolate in 40 (85%) valid specimens; physicians

could have selected appropriate antimicrobial therapy for >90% of patients on the basis of gram-staining results [75].

In haemophilus pneumonia, the Gram stain reading is even more reliable because of the profuse number of organisms that are regularly present. The finding of many WBC with no bacteria in a patient who has not already received antibiotics can reliably exclude infection by most ordinary bacterial pathogens. The validity of the gram-stain reading, however, is directly related to the experience of the interpreter [85].

Routine cultures of expectorated sputum are neither sensitive nor specific when the common bacteriologic methods of many laboratories are used. The most likely explanation for unreliable microbiological data is that the specimen did not provide a rich enough source of inflammatory material from the lower respiratory tract, either because the patient was unable to cough up a reliable specimen or because the health care provider did not give sufficient priority to obtaining such a specimen. Other reasons include prior administration of antibiotics, delays in processing the specimen, insufficient attention to separating sputum from saliva before streaking slides or culture plates, and difficulty with interpretation because of the contamination by the flora of the upper airways.

The flora may include potential pathogens (leading to false-positive cultures), and the normal flora often overgrow the true pathogen (leading to false-negative cultures), especially with fastidious pathogens such as *S. pneumoniae.* In cases of bacteremic pneumococcal pneumonia, *S. pneumoniae* may be isolated in sputum culture in only 40%–50% of cases when standard microbiological techniques are used [86, 87]. The yield of *S. pneumoniae* is substantially higher from transtracheal aspirates [88–91], transthoracic needle aspirates [89, 92], and quantitative cultures of BAL aspirates [89, 93]. Prior antibiotic therapy may reduce the yield of common respiratory pathogens in cultures of respiratory tract specimens from any source and is often associated with false-positive cultures for upper airway contaminants, such as gram-negative bacilli or *S. aureus* [62, 89].

3. Induced sputum: the utility of these specimens for detecting pulmonary pathogens other than *P. carinii* or *M. tuberculosis* is poorly established.

4. Serological studies: these tests are usually not helpful in the initial evaluation of patients with CAP (C-III) but may provide data useful for epidemiological surveillance. Cold agglutinins in a titer ≥1:64 support the diagnosis of *M. pneumoniae* infection, with a sensitivity of 30%–60%, but this test has poor specificity. IgM antibodies to *M. pneumoniae* require up to 1 week to reach diagnostic titers; reported results for sensitivity are variable [94, 95]. The serological responses to *Chlamydia* and *Legionella* species take even longer [96, 97]. The acute antibody test for *Legionella* in legionnaires' disease is usually negative or demonstrates a low titer [98, 99]. Some authorities have accepted an acute titer ≥1:256 as a criterion for a probable or presumptive diagnosis, but 1 study showed that this titer had a positive predictive value of only 15% [99].

Table 9. Diagnostic studies for specific agents of community-acquired pneumonia.

Pathogens	Rapid diagnostic test(s)[a]	Standard culture microbiological test(s)	Serology and other tests
Bacteria and bacteria-like			
Streptococcus pneumoniae	Gram-stain morphology	Expectorated sputum; uncont. specimen; bronchoscopy	Urinary antigen assay for *S. pneumoniae*
Haemophilus influenzae			
Moraxella catarrhalis			
Gram-negative bacilli			
Staphylococcus aureus			
Other			
Obligate anaerobes	Gram-stain morphology	Uncont. specimen	—
Mycoplasma pneumoniae	PCR[b]	Culture of throat or nasopharyngeal swab (rarely done, requires specialized culture techniques)	ELISA; CF; cold agglutinins
Chlamydia pneumoniae	PCR[b]	Culture of throat or nasopharyngeal swab (rarely done, requires specialized culture techniques)	MIF
Chlamydia psittaci		Usually not done (considered laboratory hazard)	CF
Legionella species	Urinary antigen assay (for *L. pneumophila* serogroup 1); PCR[a] DFA of respiratory secretions, lung tissue, or pleural fluid (primarily for *L. pneumophila* serogroup 1; some false positives with other serogroups and species)	Expectorated or induced sputum; uncont. specimen; bronchoscopy	IFA (reciprocal immunofluorescence titer $\geq$128 for *Legionella* serogroup 1; single IFA titer lacks specificity)
Nocardia species	Gram-stain morphology; modified carbol-fuchsin stain	Expectorated sputum; uncont. specimen; bronchoscopy	—
Coxiella burnetii	—	—	CF
Mycobacterium species	Acid-fast stain (fluorochrome or carbol-fuschin); PCR[a]	Expectorated or induced sputum; uncont. specimen; bronchoscopy	—
Fungi			
Pathogenic			
Histoplasma species	GMS or calcofluor white stain	Expectorated or induced sputum; uncont. specimen; bronchoscopy	CF; ID; antigen assay (blood, urine, respiratory secretions) for *H. capsulatum* antigen
Coccidioides species	Calcofluor white stain or KOH with phase contrast	Expectorated or induced sputum; uncont. specimen; bronchoscopy	CF

Blastomyces species	Calcofluor white stain or KOH with phase contrast	Expectorated or induced sputum; uncont. specimen; bronchoscopy	—
Cryptococcus species	Calcofluor white or GMS stain; antigen assay (serum)	Expectorated or induced sputum; uncont. specimen; bronchoscopy	EIA or LA for serum antigen
Opportunistic			
Candida species	Gram stain	Uncont. specimen; histology of biopsy specimen	Histology required to implicate *Candida*
Aspergillus species	GMS or calcofluor white stain	Respiratory secretion stain; uncont. specimen; histology of biopsy specimen	Allergic bronchopulmonary aspergillosis: serology; septate hyphal elements in respiratory secretions suggest *Aspergillus*
Zygomycetes species	GMS or calcofluor white stain	Respiratory secretion stain; uncont. specimen; histology of biopsy specimen	Nonseptate large hyphal elements in respiratory secretions suggest *Zygomycetes*
Pneumocystis carinii	GMS, Giemsa, or DFA stain	Induced sputum; bronchoscopy (yield much higher)	—
Viruses			
Influenza	Antigen detection (EIA); DFA stain	Virus isolation from nasopharyngeal swab	CF or HAI; ELISA; DFA; PCR
Respiratory syncytial	Antigen detection (EIA); DFA stain	Virus isolation from nasopharyngeal washing	
Adenovirus	DFA stain; PCR[a]	Virus isolation from pharyngeal swab	ELISA or RIA
Parainfluenza	DFA stain	Virus isolation from pharyngeal swab	
Varicella	Clinical: associated with skin manifestations	Virus isolation	CF (negative acute)
Herpes simplex	Typical cytopathology	Virus isolation	Histopathology (preferred)
Cytomegalovirus	Typical cytopathology of respiratory secretion (usually via bronchoscopy)	Incubation for 24 h with shell vial methodology; DFA stain or immunofluorescence of peripheral WBCs	Histopathology (preferred)
Hantavirus (see text, HPS)	PCR[b]	—	Complete blood cell count; EIA for IgG and IgM; immunohistochemistry for antigen

NOTE.   AFB, acid-fast bacilli; DFA, direct fluorescent antibody; FDA, US Food and Drug Administration; GMS, Gomori methenamine silver stain; HAI, hemagglutination inhibition; HPS, hantavirus pulmonary syndrome; ID, immunodiffusion; IFA, immunofluorescence assay; LA, latex agglutination; MIF, microimmunofluorescence; RIA, radioimmunofluorescence; uncont. specimen, uncontaminated specimen of pleural fluid, blood, transtracheal or transthoracic aspirate, or lung biopsy specimen.

[a] On respiratory secretions unless otherwise stated.

[b] PCR is available at selected reference laboratories, but reagents for detecting *M. pneumoniae* and *C. pneumoniae* are not FDA cleared. PCR is FDA cleared for detection of *Mycobacterium tuberculosis* in specimens for which smears are positive for AFB.

Table 10. Diagnostic accuracy of microbial pathogens recovered from respiratory secretions.

Diagnostic of pathogenic role, regardless of specimen source	Nondiagnostic if recovered from usual respiratory specimens[a]
Bacteria	
Legionella species	Virtually all other bacteria, including *Nocardia* and *Actinomyces* species
Mycobacteria	
Mycobacterium tuberculosis	Mycobacteria other than *M. tuberculosis*
Viruses	
Influenza	Cytomegalovirus
Respiratory syncytial	Herpes simplex virus
Hantavirus	
Parainfluenza	
Adenovirus	
Parasites	—
Strongyloides species	
Toxoplasma gondii	
Fungi	
Pneumocystis carinii	*Candida* species
Histoplasma capsulatum	*Aspergillus* species
Coccidioides	*Zygomycetes* species
Blastomyces dermatitidis	*Cryptococcus neoformans*

[a] Sputum, bronchoscopy, or nasotracheal suction.

If serological tests are to be used, an acute-phase serum specimen must be obtained from selected patients. Then, if the etiology of a case remains in question, a convalescent-phase serum can be obtained, and serological studies of paired sera can be performed. This method to identify causative agents is primarily for epidemiological information. These 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* (D-III).

5. Antigen detection: antigen-detection methods for identification of microorganisms in sputum and in other fluids have been studied for >70 years with a variety of techniques—counter-immunoelectrophoresis, latex agglutination, immunofluorescence, and enzyme immunoassay (EIA). Although their use for identification of bacterial agents (i.e., *S. pneumoniae*) has been favored in many European centers, they have been less acceptable to North American laboratories. Cost, time requirements, and relative lack of sensitivity and specificity (depending on the method) are potential limitations.

The FDA has recently approved an immunochromatographic membrane assay to detect *S. pneumoniae* antigen in urine. Results may be obtained as quickly as 15 min after initiation of the test. According to the package insert, the test has a sensitivity of 86% and a specificity of 94%. Disadvantages are the limited experience with the assay, the need for cultures in order to determine susceptibility to guide therapy, and the lack of published data on performance characteristics. The IDSA panel endorses this test as a complement to sputum and blood cultures (C-III).

The Quellung test also is a rapid assay to detect *S. pneumoniae* but requires adequate expertise. Rapid, commercially available EIAs are available for detection of respiratory syncytial virus (RSV), adenovirus, and parainfluenza viruses 1, 2,

and 3. The sensitivities of these tests are >80%. Rapid methods to detect influenza virus are of special interest because of the availability of antiviral agents that must be given within 48 h of the onset of symptoms. These tests show sensitivities of 70%–85% and a specificity >90%. Clinical detection of influenza on the basis of typical symptoms during an influenza epidemic appears more sensitive [100].

The urinary antigen tests have been shown to be sensitive and specific for detection of *L. pneumophila* serogroup 1, which accounts for ~70% of reported legionella cases in the United States [46, 98]; other possible advantages are the technical ease with which the test is performed and the validity of results after several days of effective antibiotic treatment. DFA staining of respiratory secretions is technically demanding, shows optimal results with *L. pneumophila,* and shows poor sensitivity and specificity when not performed by experts using only certain antibodies. Culture and urine antigen testing show sensitivity of 50%–60% and a specificity of >95%. A negative laboratory test does not exclude *Legionella,* particularly if the case is caused by organisms other than *L. pneumophila* serogroup 1, but a positive culture or urine antigen assay is virtually diagnostic. The IDSA panel recommends urinary antigen assays and sputum culture on selective and nonselective media, with specimen decontamination before plating, to detect legionnaires' disease (A-II).

6. DNA probes and amplification: several rapid diagnostic tests that use nucleic acid amplification for the evaluation of respiratory secretions or serum are presently under development, especially for *Chlamydia, Mycoplasma,* and *Legionella* [66]. The reagents for these tests have not been cleared by the FDA, and their availability is generally restricted to research and reference laboratories [66, 96]. If such tests become available, they may be helpful in establishing early diagnosis and allowing for directed therapy at the time of care. Their greatest potential utility is anticipated for the detection of *M. pneumoniae, Legionella,* and selected pathogens that infrequently colonize the upper airways in the absence of disease (table 9).

7. Invasive diagnostic tests (transtracheal aspiration, bronchoscopy, and percutaneous lung aspiration; table 3): transtracheal aspiration was previously used to obtain uncontaminated lower respiratory secretions that were valid for culture for the detection of anaerobic organisms, as well as common aerobic pathogens [62, 89]. This procedure is now infrequently performed because of concern about adverse effects and the lack of personnel skilled in the technique. A consequence of reduced use of transtracheal aspiration is the lack of any method to detect anaerobic bacteria in the lung in the absence of empyema or bacteremia.

The utility of fiber-optic bronchoscopy is variable, depending on pathogen and technique. Because aspirates from the inner channel of the bronchoscope are subject to contamination by the upper airway flora, they should not be cultured anaerobically, since they have the same limitations as expectorated spu-

tum [89, 101]. For recovery of common bacterial pathogens, quantitative culture of BAL or of a protected-brush catheter specimen is considered superior [102, 103]. The techniques for collection, transport, and processing of specimens for quantitative culture are available from published sources [89, 102, 103]. 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 a fulminant course, who require admission to an ICU, or have complex pneumonia unresponsive to antimicrobial therapy [89, 93, 104, 105]. Bronchoscopy is especially useful for the detection of selected pathogens, such as *P. carinii, Mycobacterium* species, and cytomegalovirus [89].

The IDSA panel recommends blood cultures and expectorated sputum Gram staining and culture as the only microbiological studies to be considered routine for patients hospitalized with CAP. Transtracheal aspiration, transthoracic needle aspiration, and bronchoscopy should be reserved for selected patients and then used only with appropriate expertise (B-III).

With regard to recommendations about diagnostic approach, table 5 lists diagnostic studies recommended for hospitalized patients, according to 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 in the English-language literature from 1966 through 1995 showed that *S. pneumoniae* accounted for two-thirds of >7000 cases in which an etiologic diagnosis was made, as well as for two-thirds of the cases of lethal pneumonia [9]. In the United States, it is estimated that 125,000 cases of pneumococcal pneumonia necessitate hospitalization each year. 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 aged ≥65 years and younger patients who have underlying medical conditions associated with increased risk for pneumococcal disease and its complications [106]. Revaccination is recommended after 5–7 years.

Until recently in the United States, *S. pneumoniae* was nearly uniformly susceptible to penicillin, which allowed clinicians to treat patients with severe pneumococcal infection with penicillin G alone or nearly any other commonly used antibiotic, 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, was found to be a major problem in South Africa in the 1970s and, subsequently, in many countries in Europe, Africa, and Asia in the 1980s. In the United States, nonsusceptibility to penicillin has increased

markedly during the last decade [107–109] and appears to be continuing [110–112].

The susceptibility of *S. pneumoniae* to penicillin is currently defined by the National Committee for Clinical Laboratory Standards (NCCLS) as follows. Susceptible isolates are inhibited by 0.06 μg/mL (i.e., the MIC is ≤0.06 μg/mL). Isolates with reduced susceptibility (also known as intermediate resistance) are inhibited by 0.1–1.0 μg/mL, and resistant isolates by ≥2.0 μg/mL. Amoxicillin is more effective than penicillin against pneumococci in vitro, with MIC thresholds that are higher. An important problem with these definitions is that, from a clinical point of view, the MIC has entirely different meaning, depending on the infection being treated. A strain with reduced susceptibility (e.g., MIC, 0.5 μg/mL) behaves as a susceptible organism when it causes pneumonia (see below) but probably not when it causes meningitis [111, 113].

On the basis of present definitions and depending on the source of the isolates, as of June 1999 in the United States, ~25%–35% of *S. pneumoniae* isolates from infected persons were intermediately resistant or resistant to penicillin [110–112]. Variations occur from city to city and within segments of the population or even within institutions in a single city, so the actual results vary greatly, depending on the source of the isolates. NCCLS definitions are based on levels achieved in CSF in cases of meningitis. Much higher levels are achieved in blood and in alveoli. For these reasons, in treating pneumonia with generally accepted doses of penicillins, intermediate resistance is not clinically important; resistance may be important, especially if it is high-grade (e.g., MIC, >4 μg/mL). Rates of resistance are substantially higher in many European countries than in the United States, with notable exceptions, such as the Netherlands and Germany; in these countries, accepted standards of practice strictly limit antibiotic usage, especially among very young children.

Resistance to penicillin is only one small part of the picture. Although the majority of strains with reduced susceptibility to penicillin are susceptible to certain third-generation cephalosporins, such as cefotaxime or ceftriaxone (defined by an MIC ≤0.5 μg/mL), intermediate resistance to these drugs (MIC, 1.0 μg/mL), and resistance (MIC, >2.0 μg/mL) are increasing [111]. In accordance with these definitions, up to one-half of strains with reduced penicillin susceptibility also have reduced susceptibility to these cephalosporins (table 11). A greater proportion exhibit resistance to other third-generation and to second-generation cephalosporins. As is the case for penicillin, pneumonia caused by intermediately resistant or even some resistant isolates is likely to respond to treatment with standard doses of cefotaxime or ceftriaxone. Cefuroxime is less active against *S. pneumoniae,* and the activity of this or other cephalosporins cannot be predicted by results of in vitro susceptibility tests with cefotaxime or ceftriaxone.

Most important, resistance extends far beyond the β-lactam antibiotics. Although the genetics of pneumococcal resistance

Table 11. Susceptibility of *Streptococcus pneumoniae* to commonly used antimicrobial agents, stratified by susceptibility to penicillin.

Agent	Susceptibility to indicated agent, per penicillin MIC category		
	≤0.1 μg/mL	0.1–1.0 μg/mL	≥2 μg/mL
Amoxicillin	+++	+++	+
Doxycycline	+++	+	+/−
Macrolide[a]	+++	+	+/−
Clindamycin	+++	++	+
TMP-SMZ	++	−	−
Cefuroxime	+++	+	−
Cefotaxime	+++	+++	+
Fluoroquinolone[b]	+++	+++	+++
Imipenem	+++	+++	−
Vancomycin	+++	+++	+++

NOTE.   In the MIC categories, the estimated percentages of pneumococci covered by the indicated agents are represented as follows: +++, ≥90%; ++, ≥75%; +, ≥50%; +/−, ≥40%; and −, <40%. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Erythromycin, clarithromycin, or azithromycin.
[b] Fluoroquinolone with improved activity against *S. pneumoniae* (e.g., levofloxacin, grepafloxacin, or trovafloxacin).

is complex, β-lactam–resistant organisms often have acquired genes that confer resistance to other classes of antimicrobials through transformation or conjugative transposons. Thus, pneumococci that are penicillin-resistant are also often resistant to other antibiotics, and the most appropriate term to characterize them is multiply antibiotic-resistant (table 11; these data reflect the general situation in the United States as of October 1999). Resistance to some of these antimicrobials can be overcome by increasing the dose of antibiotic.

Macrolides are an example. In the United States, most macrolide resistance is a result of increased drug efflux encoded by *mefE* (erythromycin MIC, 2–32 μg/mL, and susceptible to clindamycin); it is possible that this resistance may be overcome by achievable levels of macrolides [114]. In Europe, most macrolide resistance is due to a ribosomal methylase encoded by *ermAM;* this results in high-grade resistance to macrolides and resistance to clindamycin that probably cannot be overcome. It is important to emphasize that resistance to newer macrolides, such as azithromycin or clarithromycin, parallels resistance to erythromycin. The prevalence of resistance to tetracyclines among pneumococci is similar to that of resistance to macrolides, but resistance to trimethoprim-sulfamethoxazole (TMP-SMZ) is far more prevalent, and use of this combination is discouraged [109–112]. Among FDA-approved drugs, only vancomycin and linezolid are currently effective against essentially all pneumococci. Fluoroquinolones are active against >98% of strains, including penicillin-resistant strains, but resistance to these drugs has begun to increase in some areas where they are used extensively [115–118]. Of the newer drugs, the oxazolidinones [119] and glycopeptides [120] appear to be most promising, with MICs for drug-resistant *S. pneumoniae* being no higher than those for penicillin-susceptible strains. Resistance to the streptogramins appears to parallel that to the macrolides.

Studies of oral outpatient therapy for pneumonia, in which the majority of cases have probably been due to *S. pneumoniae,* have shown a good outcome, regardless what therapy is given; however, these studies were not designed to examine antibiotic resistance among pneumococci. Recommended antimicrobial agents for empirical treatment of pneumococcal pneumonia include amoxicillin (500 mg thrice daily), cefuroxime axetil (500 mg twice daily), cefpodoxime (200 mg twice daily), cefprozil (500 mg twice daily), and azithromycin, clarithromycin, erythromycin, or a quinolone or doxycycline in ordinarily prescribed dosages. Amoxicillin is preferred to penicillin because of more reliable absorption, longer half-life, and slightly more favorable MICs. Although recent surveillance studies indicate increasing resistance to macrolides, to date there is a paucity of reports of clinical failure in patients without risk factors for infection with drug-resistant *S. pneumoniae* [114]. With increasing use, however, there is concern about reduced efficacy of macrolides.

In hospitalized patients, pneumococcal pneumonia caused by organisms that are susceptible or intermediately resistant to penicillin responds to treatment with penicillin (2 million units every 4 h), ampicillin (1 g every 6 h), cefotaxime (1 g every 8 h), or ceftriaxone (1 g every 24 h). Pneumonia due to penicillin- or cephalosporin-resistant organisms probably requires higher doses of these drugs. Retrospective studies [121, 122] have shown a similar outcome after treatment with standard doses of a penicillin or a cephalosporin, without regard to whether pneumonia was due to susceptible or nonsusceptible organisms, but the number of subjects infected with resistant pneumococci (MIC, ≥2 μg/mL) was very small, and there was a trend toward worse outcomes in both studies [121, 122].

A CDC study found mortality associated with treated pneumococcal pneumonia to be increased 3-fold when the condition was due to penicillin-resistant pneumococci and 7-fold when due to ceftriaxone-resistant pneumococci, even after adjusting for severity of underlying illness and previous hospitalization, both of which increase the likelihood that resistant pneumococci will be present [123]. This study, however, did not determine the nature of the treatment in each case. It seems likely that, ultimately, penicillin or ceftriaxone may not reliably cure infection caused by strains of *S. pneumoniae* for which penicillin MICs are ≥4 μg/mL and ceftriaxone MICs are ≥8 μg/mL.

At present, many authorities treat pneumococcal pneumonia, even in critically ill patients, with cefotaxime (1 g every 6–8 h) or ceftriaxone (1 g every 12–24 h). Many patients have received 1–2 g of ampicillin (with or without sulbactam) every 6 h, with a good response. Although vancomycin is nearly certain to provide antibiotic coverage, there is a strong impetus not to use this drug until it is proven to be needed because of fear of the emergence of resistant organisms. Vancomycin or a fluoroquinolone should be used for initial treatment of pneumococcal pneumonia in critically ill patients who are allergic to β-lactam antibiotics. Quinupristin/dalfopristin or linezolid are other op-

Table 12.   Characteristics of the various forms of aspiration pneumonia.

Inoculum	Pulmonary sequelae	Clinical features	Therapy
Acid	Chemical pneumonitis	Acute dyspnea, tachypnea, tachycardia with or without cyanosis bronchospasm, fever; sputum: pink, frothy; radiograph: infiltrates in one or both lower lobes; hypoxemia	Positive-pressure breathing, iv fluids, tracheal suction
Oropharyngeal bacteria	Bacterial infection	Usually insidious onset; cough, fever, purulent sputum; radiograph: 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

tions, but experience with these antimicrobial agents for pneumococcal pneumonia is extremely limited.

Aspiration Pneumonia

Aspiration pneumonia is broadly defined as the pulmonary sequela of abnormal 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 3 distinctive forms [124], based on the nature of the inoculum, the clinical presentation, and management guidelines: toxic injury of the lung (such as due to gastric acid aspiration or Mendelson's syndrome), obstruction (with a foreign body or fluids), or infection (table 12). These syndromes are reviewed elsewhere [125, 126]. Most studies show that aspiration is suspected in 5%–10% of patients hospitalized with CAP, although the criteria for this diagnosis are often not provided. In general, the diagnosis should be suspected when patients have a condition that predisposes them to aspiration (usually compromised consciousness or dysphagia) and radiographic evidence of involvement of a dependent pulmonary segment (lower lobes are dependent in the upright position; 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 infection, and microaerophiles and anaerobes from the mouth flora are the anticipated pathogens in bacterial infections associated with aspiration.

Anaerobic Bacterial Infections

The frequency of infection that involves anaerobes among patients with CAP is not known, because the methods required to obtain uncontaminated specimens that are valid for anaerobic culture are rarely used. The usual specimens are transtracheal aspirates, pleural fluid, transthoracic needle aspirates, and uncontaminated specimens from metastatic sites [89, 127, 128]; a limited experience suggests that quantitative cultures of protected-brush or BAL specimens collected at bronchoscopy may

be acceptable [89, 102, 103, 127]. Anaerobic and microaerophilic bacteria are the most common etiologic agents of lung abscess and aspiration pneumonia and are relatively common isolates in empyema [126]. Characteristically, many bacterial species are isolated from infected tissues. Patients with anaerobic bacterial infection may also present with pneumonitis that is indistinguishable from other common forms of bacterial pneumonia on the basis of clinical features [129].

Clinical clues to this diagnosis 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 [126]. Anaerobes may also account for a substantial number of cases of CAP that do not have these characteristic features [102, 126, 130]. With regard to therapy, the only comparative therapeutic trials for anaerobic lung infections have been with lung abscess, and these show clindamycin to be superior to iv penicillin [130, 131]. Using metronidazole alone as antimicrobial therapy is associated with a high failure rate, presumably because of the role played by facultative and microaerophilic streptococci.

Amoxicillin-clavulanate (A-I) also appears to be effective [132]. Antibiotics that are virtually always active against anaerobes in vitro include imipenem, meropenem, metronidazole, chloramphenicol, and any combination of a β-lactam/β-lactamase inhibitor. Moxifloxacin, gatifloxacin, and trovafloxacin also have good in vitro activity against most anaerobes. Macrolides, cephalosporins, and doxycycline have variable activity. TMP-SMZ and aminoglycosides are not active against most anaerobes.

The IDSA panel recommends clindamycin, a β-lactam/β-lactamase inhibitor, imipenem, and meropenem as preferred drugs for treating pulmonary infections when anaerobic bacteria are established or suspected as the cause (B-I).

C. pneumoniae Pneumonia

Although prevalence varies from year to year and within geographic settings, *C. pneumoniae* causes ~5%–15% of cases

of CAP [8, 39, 40, 133–135]; the majority of cases of pneumonia are relatively mild and associated with low mortality [133, 134]. *C. pneumoniae* pneumonia may present with 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* usually occurs for older patients who have reinfection, in which comorbidities undoubtedly play a significant role in the clinical course. When *C. pneumoniae* is found in association with other pathogens, particularly *S. pneumoniae,* the associated pathogen appears to determine the clinical course of the pneumonia [133]. Infection can be suspected with culture of *C. pneumoniae,* DNA detection and PCR, and serology (most specifically by microimmunofluorescent antibodies) [66, 96, 133–135]. However, cell culture is not routinely available except in research laboratories; in addition, PCR technology is not standardized, reagents for PCR are not FDA cleared, and serology is problematic because of nonspecificity [66, 136]. The preferred diagnostic finding is documentation of a 4-fold increase in titer from acute to convalescent specimens, with supporting evidence by PCR or culture. Accordingly, most laboratories cannot confirm a diagnosis of *C. pneumoniae* pneumonia in a timely fashion, so treatment must be empirical (A-II). For therapy, the IDSA panel recommends a macrolide, doxycycline, or a fluoroquinolone (B-II) [134, 137].

Legionnaires' Disease

Legionella is implicated in 2%–6% of CAP cases in most hospital-based series; some groups report higher rates that presumably reflect local epidemiology and/or more sensitive laboratory techniques [8, 39–41, 138]. Risk is related to exposure, increasing age, smoking, and compromised cell-mediated immunity such as in transplant recipients [46]. Although rare in immunocompetent adults aged <30 years, *Legionella* can be a major cause of lethal pneumonia, with mortality rates of 5%–25% among immunocompetent hosts and substantially higher rates among immunosuppressed hosts [46, 138]. Tests commonly cost $50–$100 each, so routine use for hospitalized patients is not usually advocated (table 9). Major indications for testing include severe illness in adults requiring admission to the ICU, pneumonia in hospitalized patients with no other likely etiology (i.e., negative Gram stain), pneumonia in compromised hosts, evidence suggesting *Legionella* is endemic or epidemic in the area, lack of response to β-lactam antibiotics, or clinical features that suggest *Legionella* as the cause (C-III) [99].

Epidemiological risk factors for legionnaires' disease include recent travel with an overnight stay outside the home, recent changes in domestic plumbing, renal or hepatic failure, diabetes, and systemic malignancy [46]. Some authorities feel that the following constellation of clinical features suggests this diagnosis: high fever, hyponatremia, CNS manifestations, lactate

dehydrogenase levels >700 units/mL, or severe disease [138]. Methods of laboratory detection include culture, serology, DFA staining, urinary 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-cleared reagents. Tests recommended by the IDSA panel are urinary antigen assay for *L. pneumophila* serogroup 1, which is not technically demanding and reliably and rapidly detects up to 70% of cases of legionnaires' disease, and culture on selective media, which detects all strains but is technically demanding [46, 139] (B-II).

Historically, the preferred therapeutic agent has been erythromycin, usually in a total daily dose of 2–4 g iv, with or without rifampin (600 mg po q.d.); erythromycin (500 mg po q.i.d., to complete 2–3 weeks of treatment) can be substituted after there has been clinical response. Many authorities now consider azithromycin or a fluoroquinolone to be preferred for severe disease. This preference is based on results superior to those with erythromycin in animal models and, in addition, on poor tolerance of erythromycin [46, 140, 141]. FDA-approved drugs for administration against *Legionella* are erythromycin, azithromycin, ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, and gatifloxacin. A delay in therapy is associated with increased mortality [142]. The IDSA 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, although less for azithromycin because of its long half-life.

HPS

HPS is a frequently lethal systemic disease of previously healthy young adults that was originally recognized in May 1993. At least 5 viruses have been implicated [143–145]. The most common in the United States is Sin Nombre virus, which is carried by the deer mouse. 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 [146]. The median age of patients for the first 100 United States cases was 35 years, and the overall case fatality rate was 52% [147]. 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, chest radiographic evidence of capillary leakage (adult respiratory distress syndrome [ARDS]), and oxygen desaturation. Other, more common causes of ARDS for consideration are chronic pulmonary disease, malignancy, trauma, burns, and surgery. Among lethal cases of HPS, the median time of death

is 5 days after onset of the disease. Typical laboratory findings include hemoconcentration, thrombocytopenia, leukocytosis with a left shift, and circulating immunoblasts. Additional laboratory findings include an elevated serum lactate dehydrogenase level, arterial partial pressure of oxygen <90 mm Hg, and increased serum lactate level.

The diagnosis is established by detection of hantavirus-specific IgM, increasing titers of hantavirus-specific IgG, hantavirus-specific RNA (by PCR) in clinical specimens, or hantavirus antigen (by immunohistochemistry) [139, 147]. These laboratory tests should be performed or confirmed at a reference laboratory. Treatment consists of supportive care that often requires intubation and mechanical ventilation with positive end-expiratory pressure. These patients also require hemodynamic support. Ribavirin inhibits Sin Nombre virus in vitro, but the initial clinical experience has been disappointing. A controlled trial is ongoing.

M. pneumoniae Pneumonia

M. pneumoniae is a common cause of respiratory tract infections, primarily in those aged 5–9 years and in young adults. This organism causes a small percentage of cases of CAP requiring hospitalization [2, 8, 39–40, 47, 48]. The incubation period is 2–4 weeks, so epidemics in closed populations evolve slowly. The most common presentation is tracheobronchitis; ~3% of patients who are acutely infected with *Mycoplasma* have pneumonia demonstrable by chest radiography. Common symptoms with pneumonia include a prodromal period with fever, chills, headache, and sore throat, followed by a cough that is dry or produces mucoid sputum [47, 148]. 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; vomiting; and, rarely, myocarditis, skin rash, and, diverse neurological syndromes.

Laboratory tests to confirm infection due to *M. pneumoniae* include culture, serology, and PCR [48, 66, 94, 95]. Fastidious growth requirements and long incubation periods limit utility of culture, and most laboratories do not offer this test. IgM and IgG antibody values become elevated in most cases, but the response is often delayed, so the utility of these tests for early detection is limited, and reported results are variable [94, 95]. Some authorities consider PCR to be particularly promising [66, 94]. Current problems with amplification techniques include great variability due to differences in methods of sample collection, sample preparation, and amplification procedures; there are also no FDA-cleared reagents for PCR for detection of *Mycoplasma*.

Cold agglutinin titers ≥1:64 support this diagnosis, and the cold agglutinin response correlates with the severity of pulmonary symptoms, but the test lacks both sensitivity and specificity. It is suggested that a single CF antibody titer ≥1:64, combined with a cold agglutinin titer ≥1:64, supports this diagnosis [47, 48]. The antibody response usually develops at 7–10 days after the onset of symptoms and shows peak levels at ~3 weeks. Changes on chest radiography are nonspecific. Most common is a unilateral infiltrate, but one-third of patients have bilateral changes. The IDSA panel concludes that no available diagnostic test reliably and rapidly detects *M. pneumoniae*. Thus, therapy must usually be empirical (B-II).

The panel recommends treatment with tetracycline or a macrolide for most cases; an alternative is a fluoroquinolone (B-III). Treatment should be given for 2–3 weeks to reduce the risk of relapse. The role of antibiotic therapy for extrapulmonary manifestations is not established.

P. carinii Pneumonia (PCP)

PCP is not included in the guidelines for management of CAP in the immunocompetent host because it 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 still be unaware of the underlying infection. One study of 385 consecutive hospitalizations for CAP in an urban hospital in 1991 showed that 46% of patients had HIV infection, and 19% of these patients were unaware of their HIV status at the time of admission [40]. 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 nonproductive cough, fever, and dyspnea that evolve over a period of weeks. The average patient has had pulmonary symptoms for 4 weeks at the time of initial presentation; this relatively slow tempo of disease distinguishes PCP in patients with AIDS from common forms of bacterial pneumonia. The usual associated laboratory features include lymphopenia (total lymphocyte count, <1000 cells/mL), CD4 lymphopenia (<200 cells/mL in >95% of patients), arterial hypoxemia, and chest radiographic evidence of bilateral interstitial infiltrates with a highly characteristic "ground glass" appearance. Up to 30% of patients have negative chest radiographs, which makes this illness the only relatively common form of pneumonia associated with false-negative chest radiographs [149]. The diagnostic yield with induced sputum averages 60% but varies greatly, depending on quality control [150]. The yield with bronchoscopy exceeds 95%.

The disease is uniformly fatal if not treated. TMP-SMZ, dapsone-trimethoprim, and clindamycin-primaquine appear to be equally effective for treating patients who have moderately severe disease [151]. No currently recommended therapy for CAP is probably effective for PCP. The mortality rate among

treated patients who are hospitalized is usually reported to be 15%–20%.

Influenza

Influenza is clearly the most common serious viral airway infection of adults in terms of morbidity and mortality. Seasonal epidemics in the United States are commonly associated with ⩾20,000 deaths that are ascribed to this infection and its complications, primarily bacterial superinfections. The great pandemics of influenza in the past century were of "Spanish flu," which in 1918 was responsible for >20 million deaths worldwide, Asian influenza (1957), and Hong Kong influenza (1968) [152]. The great majority of deaths in annual influenza epidemics are of patients who are aged >65 years, and a disproportionate number are of residents of chronic care facilities. The most common cause of bacterial superinfection is *S. pneumoniae;* in an era when *S. aureus* was the principal cause of hospital-acquired infection, this organism was prevalent [153].

Rapid identification tests are available and can lead to an etiologic diagnosis in 15–20 min with a sensitivity of 70%–90% [100]. A diagnosis can often be made with comparable sensitivity on the basis of typical symptoms in nonvaccinated patients during an influenza epidemic. In general, influenza A is more severe and shows greater antigenic heterogeneity than does influenza B. Amantadine or rimantadine appears to reduce the duration and severity of symptoms in patients with influenza A, but these drugs have no activity against influenza B [154]. Zanamivir [155–157] and oseltamivir [158] are active against influenza A and B viruses. The relative efficacy of these neuraminidase inhibitors versus that of amantadine and rimantadine for treating or preventing influenza A is unknown [158]. Clinical trials to date show that all 4 drugs reduce the duration of fever by 1–1.5 days when given within 48 h of the onset of symptoms.

All 4 antimicrobial agents are also effective in influenza prevention, but the most effective prophylaxis is with annual administration of vaccine, which has been shown to have efficacy of >60% for preventing transmission in 10 of the last 11 influenza seasons. Efficacy for prevention is reduced in elderly residents of chronic care facilities, but effectiveness in preventing mortality is often reported to be 70%–80% in this latter population, depending, to some extent, on the match between the epidemic strain and the constituents of the vaccine [159]. A provocative report suggests that vaccination of health care providers in chronic care facilities is as important, or more important, than vaccination of the patients [160]. Another report showed an 88% rate of vaccine efficacy and reduced absence for respiratory illness among hospital-based health care workers [161]. These data emphasize the importance of vaccine strategies that target the populations at greatest risk, including persons aged ⩾65 years, 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 recent investigators have used pleural fluid analyses; a pleural effusion with a pH <7.2 usually indicates a need for drainage [162]. This complication occurs in 1%–2% of all cases of CAP and in up to 5%–7% of hospitalized patients with CAP [163, 164]. The incidence of empyema has decreased substantially from the preantibiotic era, when *S. pneumoniae* accounted for about two-thirds of cases, and the bacteriology also has changed. A meta-analysis of 1289 cases of empyema reported during 1970–1995 shows that *S. pneumoniae* now is isolated in only 5%–10% of cases; the majority involve anaerobic bacteria, *S. aureus,* and/or gram-negative bacilli [165]. Many are mixed infections. It is uncertain in how many culture-negative cases are caused by pneumococci that were eradicated by prior antibiotic treatment.

Most studies of CAP show that up to 57% of patients have pleural effusions identified by routine chest radiography [166]. Empyema is infrequent in these patients, but it is important to recognize because of its implications regarding the need for adequate drainage as a critical component of effective management. Some authorities recommend thoracentesis for any parapneumonic effusion that measures >10 mm on a lateral decubitus radiograph [166]. Standard tests to be performed on pleural fluid include appropriate stains and culture for aerobic and anaerobic bacteria, as well as measurement of pH, lactic dehydrogenase concentration, and leukocyte and differential counts. Particularly important is the pH determination, for which the fluid must be obtained anaerobically, placed on ice, and transported immediately to the laboratory. Drainage is required when there is pus in the pleural space, a positive Gram stain or culture, or a pH <7.2. Neither the lactic dehydrogenase level nor the glucose level is as sensitive as pH for this prediction.

The drainage may be done with a chest tube, image-guided catheters, thoracoscopy, or thoracotomy. The relative merits and indications for use of image-guided chest tubes, catheters with thrombolytics, and thoracoscopic or thoracotomy decortication are not well defined.

AB

AB is one of the most common yet least understood (and overtreated) problems seen in an outpatient setting. Bronchitis ranks among the most common conditions seen in an outpatient setting, accounting for ~42% of all primary diagnoses assigned for patients with cough (compared with 5% for pneumonia) [167]. Because clinical manifestations of AB may be similar to those of pneumonia, distinguishing between these conditions by chest radiography is paramount to optimizing therapy.

AB is generally used to describe a transient (usually <15 days' duration) respiratory illness that occurs among patients without

chronic lung inflammatory conditions and is characterized by cough (with or without sputum, fever, and/or substernal discomfort) and in the absence of radiographic findings of pneumonia. However, there is no clear consensus on the definition of AB. The lack of a standardized case definition of AB or established value of microbiological studies and the high rate of spontaneous resolution interfere with the establishment of a firm diagnosis and rational implementation of appropriate treatment [52, 168].

The differential diagnosis of cough requires consideration of both infectious and noninfectious etiologies. Among noninfectious causes are smoking, asthma, postnasal drip syndrome, angiotensin-converting enzyme inhibitors, and pollutants. Cough due to infection includes a spectrum of conditions, such as nasopharyngeal infection (common cold), AB, chronic bronchitis, sinusitis, and pneumonia. A better understanding that cough (even with sputum or if prolonged) is an expected part of uncomplicated viral respiratory infection and not necessarily indicative of bacterial infection should help practitioners and patients avoid unnecessary antimicrobial use [169, 170]. Approximately 40% of persons experimentally infected with rhinovirus experience cough as a prominent symptom. The cough persists longer than other symptoms; in fact, after 14 days, ~20% of such patients still have cough [170]. Auscultatory findings are nonspecific and are often normal, but variable findings, such as localized rales, wheezing, and prolonged expiratory phase, may be noted, especially in patients with reactive airway disease.

Distinguishing AB from nonserious pneumonia has important therapeutic and prognostic implications. Published studies of pneumonia indicate that no combination of clinical findings can reliably define the presence of pneumonia [171]. Although the absence of any vital sign abnormality or any abnormalities on chest auscultation substantially reduces the likelihood of pneumonia, this constellation of findings does not rule out this illness. Therefore, the only standard criterion to differentiate these conditions is chest radiography.

The syndrome of AB is most often associated with respiratory viruses for which antibacterial therapy is unwarranted [51, 52, 172, 173]. However, no well-controlled studies that use modern diagnostic methods have been performed recently that would enable systematic evaluation of the role of respiratory pathogens. The most common viruses identified have been the common cold viruses, rhinovirus and coronavirus; others include influenza virus, adenovirus, parainfluenza virus, and RSV. A small proportion of cases are of nonviral etiology. *M. pneumoniae, C. pneumoniae,* and *Bordetella pertussis* have been linked to AB [174]. There is little evidence that *S. pneumoniae* or *H. influenzae* has an important role in the etiology of AB in adults with community-acquired infections in the absence of chronic obstructive lung disease, airway violation (e.g., tracheostomy), immunosuppression (e.g., AIDS), or serious associated disease, such as cystic fibrosis. For persons with acute

exacerbation of chronic obstructive pulmonary disease, semiquantitative analysis of sputum by microscopic examination and culture suggest that *H. influenzae* and *S. pneumoniae* may be in greater concentrations than in the absence of exacerbation [175]. The data, however, are inconsistent [176], and most exacerbations appear to be due to factors other than bacterial infection.

The value of antibacterial agents in the treatment of immunocompetent patients with AB has not been confirmed, and the use of these agents is not recommended. Several controlled trials suggest that antibiotics for the majority of patients with cough due to AB are of no measurable benefit [51, 52, 166, 177–179]. Conflicting results of clinical trials may be explained by variations in methodology and patient type (including patients with acute exacerbations of chronic bronchitis). In contrast, some studies have demonstrated bronchodilators (e.g., albuterol) to be more effective than antibiotics for the relief of symptoms [177, 178].

Despite information that antibiotics are generally not indicated for AB, studies indicate that primary care providers use them in the majority of cases [55]. This overuse of antibiotics increases the pressure that leads to antimicrobial resistance. Several reasons are given to justify use of antibiotics in AB: (1) patients' expectations; (2) the possible benefit of preventing secondary bacterial infection; and (3) the possibility of treatable causes (i.e., infections with *Mycoplasma* or *Chlamydia*). It must be remembered that there are no data showing that treatment against these organisms has a favorable effect in bronchitis. In addition, a recent study found that patients' satisfaction did not depend on receipt of an antibiotic prescription, as long as physicians explained the rationale for management [180], and another study showed that antibiotic abuse in cases of AB was reduced when both physicians and patients were warned of the consequences of this practice [52].

Numerous studies support this recommendation, including a meta-analysis that showed only a slight benefit was gained with antibiotic therapy. The authors concluded that the disadvantages of antibiotics outweigh this modest benefit [181]. Until cost-effective, accurate, and rapid diagnostic tests (i.e., PCR of throat swab specimens) are available to confirm causes such as *Mycoplasma* or *Chlamydia,* the IDSA panel recommends reserving antibiotic therapy (i.e., with macrolides or tetracyclines) for patients with severe or persistent disease (e.g., >14 days' duration) [164] and then only if there is a reasonable likelihood of pertussis [182]. (The rationale for antibiotic treatment late in the course of pertussis is to reduce transmission.)

The IDSA panel agrees with others in encouraging all physicians to identify methods to decrease unnecessary antimicrobial use for AB by improving their clinical approach or by communicating with patients concerning the lack of benefit, possible side effects, and development of resistance associated with such therapy [52, 166]. The practice of withholding antibiotics to most patients with cough illness is supported by the

Table 13. Biological warfare agents that would cause pulmonary disease.

Feature	Anthrax	Plague	Tularemia
Putative agent	*Bacillus anthracis*	*Yersinis pestis*	*Francisella tularensis*
Estimated casualties with 50 kg of aerosol over metropolitan area with 5 million persons[a]	250,000 (100,000 would die without treatment)	150,000 (36,000 would die without treatment)	250,000 (17,000 would die without treatment)
Mean incubation period (range)	2–6 d (1–42 d)	2–5 d (1–6 d)	3–5 d (1–21 d)
Clinical findings	Fever, malaise, cough, followed by ARDS and shock	Fever, malaise, cough ± bloody sputum, followed by shock	Fever, prostration, cough
Laboratory findings	Radiographic evidence of widened mediastinum; leukocytosis	Radiographic evidence of patchy or consolidated infiltrate; leukocytosis; DIC	Radiographic evidence of focal pneumonia + hilar nodes
Diagnosis	(1) Gram stain of unspun peripheral blood; (2) positive blood culture (sputum culture negative)	Gram-negative bipolar coccobacillus on stain and culture of blood, sputum, CSF	Culture of blood, sputum, and pharyngeal specimen (high risk to laboratory personnel; use BL-3 facility in suspected cases)
Treatment	Ciprofloxacin (alternatives: other fluoroquinolones,[b] doxycycline, or penicillin, if susceptible)	Streptomycin or gentamicin (alternatives: tetracyclines or fluoroquinolones[b])	Doxycycline; streptomycin (or gentamicin); chloramphenicol
Duration of therapy	60 d	10 d	14 d
Isolation	Standard (no person-to-person spread)	Respiratory precautions until treated for 48 h	Standard (person-to-person spread is rare)
Mortality	>95% without therapy; 80% with therapy	~100% unless treated in <24 h	35% without treatment; 1%–2% with treatment
Prophylaxis after exposure	Ciprofloxacin, amoxicillin, or doxycycline	Doxycycline or fluoroquinolone[b]	Doxycycline
Duration of prophylaxis	60 d	7 d	14 d
Vaccine	Likely to be effective in postexposure setting, but no vaccine is currently available for civilian use	Not effective for plague pneumonia	Live vaccine is investigational new drug under study
Person-to-person transmission	None	Patient can be contagious to close contacts until treated for 48 h	None

NOTE. Table is adapted from [184]. ARDS, adult respiratory distress syndrome; DIC, diffuse intravascular coagulation; ±, with or without.
   [a] Estimate from [185].
   [b] Ciprofloxacin, levofloxacin, ofloxacin, grepafloxacin, or sparfloxacin.

literature and is not associated with an increase in office visits [52]. The cost of follow-up visits for those patients whose conditions do not improve over a few days should be balanced against the high likelihood of spontaneous resolution and the risk to the patients and the community of unnecessary antibiotic use [165]. An exception to this admonition is consideration of an anti-influenza agent administered within 48 h of the onset of symptoms.

Pneumonia in the Context of Bioterrorism

There is increasing appreciation of the potential for bioterrorism, either from dissidents or from foreign countries. The relevance of this to pneumonia guidelines is based on the observation that several microbes that could be used as weapons would be expressed as pneumonia. A number of microbes could be disseminated as biological weapons by aerosol as an invisible, odorless, tasteless inoculum that could afflict as many as thousands of patients after an incubation period of days to weeks. In this setting, the etiologic agents most likely to cause severe pulmonary infection are *Bacillus anthracis, Yersinia pestis,* and *F. tularensis* [183, 184] (table 13). Recognition of these conditions would be by medical practitioners, and it is critical to implement appropriate strategies to establish the diagnosis, treat afflicted patients, and provide preventive treatment to

those exposed. Thus, the "first responders" for bioterrorism are expected to be physicians in office practice, emergency rooms, ICUs, and in the discipline of infectious diseases. It should be acknowledged that national planning for a civilian medical and public health response is only now being initiated.

B. anthracis, the cause of inhalational anthrax, is one of the organisms that could be used for biological terrorism that causes the most concern because of the environmental stability of its spores, the small inoculum necessary to produce fulminant infection, and the high associated mortality rate. The incubation period is quite variable—most cases present in the first several days after exposure, but the incubation period can be ⩾6 weeks [186]. The initial symptoms are nonspecific, with fever, malaise, chest pain, and a nonproductive cough. This may be followed by brief improvement and then severe respiratory distress, shock, and death.

This is not a true pneumonia; chest radiographs most often show a highly characteristic widened mediastinum without parenchymal infiltrates. The diagnosis is established with positive blood cultures that may be initially dismissed as having a "*Bacillus* contaminant," unless there are multiple such "contaminants" in a single facility; sputum cultures are negative. The mortality rate without treatment is >95%. In fact, the mortality rate remains >80% if treatment is not initiated before the de-

velopment of clinical symptoms [187]. Administration of iv penicillin in high doses has historically been considered the preferred therapy, but reports of engineered resistance have been published. Thus, empirical treatment before sensitivity tests of the responsible strain should be oral or iv ciprofloxacin, with doxycycline or penicillin as an alternative.

Sensitivity tests for initial cases may be used to dictate antibiotic choices for subsequent patients. Treatment should be continued for 60 days because of the potential problem of prolonged incubation, with delayed but equally lethal disease. Since no human-to-human transmission occurs, standard isolation precautions are appropriate. Particularly important will be prophylaxis for those who are in the region of exposure; determining the population at risk will require emergent assessment by public health officials. The preferred regimens are ciprofloxacin (500 mg po b.i.d.), doxycycline (100 mg po b.i.d.), or amoxicillin (500 mg po q8h), depending on susceptibility of the epidemic strain. Prophylaxis should be continued for 60 days. Ciprofloxacin and doxycycline are advocated, because they are highly active in vitro and have established efficacy in the animal model [186]. Other fluoroquinolones are probably equally effective. These factors are emphasized because of the possibility that regional supplies may be limited with large-scale exposures.

F. tularensis causes <200 infections per year in the United States but caused hundreds of thousands of infections in Europe in World War II. Its potential as a biological weapon was substantiated by extensive studies performed by the US biological weapons program in the 1960s. There are multiple forms of disease, but the most common following aerosol exposure is "typhoidal" or "pneumonic" tularemia. The average incubation period is 3–5 days (table 13). Symptoms are nonspecific and include fever, malaise, and nonproductive cough. Chest radiographs show evidence of pneumonia with or without mediastinal adenopathy. If tularemia is suspected, the organism may be cultured from blood, sputum, or pharyngeal exudates, but only with difficulty. Culture media that contains cysteine or other sulfhydryl compounds should be used.

This organism represents a hazard to laboratory personnel, and culture should be attempted only in a BL-3 laboratory. The usual method for diagnosis is serology, which is positive in the second week of disease in 50%–70% of cases. Standard treatment is with streptomycin or gentamicin; tetracycline and chloramphenicol are also effective but are associated with higher rates of relapse. Tetracycline has been used effectively as postexposure prophylaxis. There is minimal risk of person-to-person spread. The recommendation for prophylaxis for exposed persons is administration of tetracycline or doxycycline for 2 weeks.

Y. pestis is also a potential biological weapon of great concern because of it has a fulminant course of infection, causes death in the absence of antibiotic treatment, and can be spread from person to person. Clinical features of pneumonia plague include high fever, chills, headache, cough, bloody sputum, leukocy-

tosis, and radiographic changes that show bilateral pneumonia, with rapid progression to septic shock and death (table 13). The acutely swollen, tender lymph node or bubo that is highly characteristic of bubonic plague is unlikely to be present. The diagnosis is established with culture of sputum or blood; sputum Gram stain shows typical safety-pin, bipolar-staining gram-negative coccobacilli.

Health care workers are at risk for aerosol exposure, so respiratory precautions should be taken until patients have had 48 h of therapy. The standard treatment for plague pneumonia is administration of streptomycin or gentamicin in standard doses for 10 days [187]. Alternatives for the mass-casualty setting are tetracyclines or fluoroquinolones given orally for 10 days. Administration of tetracyclines or fluoroquinolones for 7 days is the preferred prophylaxis when face-to-face contact has occurred or exposure is suspected. The licensed plague vaccine has not been found to protect against or ameliorate pneumonic plague and has no role in this setting.

Management

Management recommendations within this document are restricted to immunocompetent adults with acute CAP and are stratified on the basis of whether patients are treated as outpatients or are hospitalized (figure 2). Emphasis is 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 an expectorated sputum specimen collected (in the presence of the physician whenever possible) before antimicrobial administration, unless these procedures would substantially delay initiation of treatment (B-II). Consensus is lacking as to the need for microbiological diagnosis for outpatients, although preparation of an air-dried, heat-fixed slide of sputum (obtained before antimicrobial treatment for subsequent Gram staining) is desirable. Investigation for selected microbial pathogens, such as *Legionella* and *Mycobacterium,* will depend on clinical features.

2. Pathogen-directed antimicrobial therapy: an attempt should be made to achieve pathogen-directed antimicrobial therapy for hospitalized patients (C-III; table 14). This decision should be made when relevant information becomes available, and its strength is greatest in cases when an established etiologic agent has been identified, according to criteria described above. Empirical selection of antimicrobial agents, when necessary, should be directed against the pathogens that are most common and treatable, according to the setting (table 15). Antibiotic regimens selected empirically should be changed when results of culture and in vitro sensitivity tests become available, on the assumption that clinical and microbiological correlations support this tactic.

3. Prompt antimicrobial treatment: antimicrobial treatment should be initiated promptly after the diagnosis of pneumonia
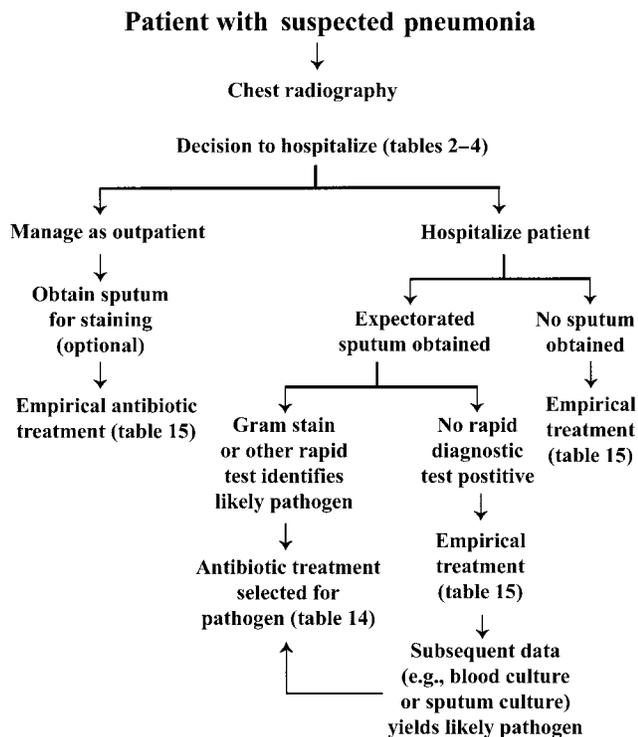
Patient with suspected pneumonia

↓

Chest radiography

Decision to hospitalize (tables 2–4)

Manage as outpatient   **Hospitalize patient**

↓

Obtain sputum for staining (optional)

Expectorated sputum obtained   **No sputum obtained**

↓

Empirical antibiotic treatment (table 15)

Gram stain or other rapid test identifies likely pathogen   **No rapid diagnostic test postitive**   **Empirical treatment (table 15)**

↓

Antibiotic treatment selected for pathogen (table 14)

Empirical treatment (table 15)

↓

Subsequent data (e.g., blood culture or sputum culture) yields likely pathogen

Figure 2. Procedures for diagnosis and for outpatient and hospital-centered management of community-acquired pneumonia in adults.

is established with radiography and after 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; an analysis of 14,000 patients showed that a >8-h delay from the time of admission to initiation of antibiotic therapy was associated with an increase in mortality (B-II) [188]. 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 based on prognostic criteria, as summarized in table 4 (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. Studies show that 25%–50% of admissions for CAP are for these other considerations, which extend beyond those listed as admission criteria in table 4 [10, 36].

Management of Patients Who Do Not Require Hospitalization

Diagnostic studies. The diagnosis of pneumonia requires the demonstration of an infiltrate on chest radiography. Posteroanterior and lateral chest radiography is recommended

when pneumonia is suspected (A-II), although obtaining these radiographs may not always be practical. Additional diagnostic studies for patients who are candidates for hospitalization are summarized in table 5 (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 cell count with differential is sometimes useful to assess the illness further, in terms of detecting the severity of the infection, presence of associated conditions, and chronicity of infection.

Pathogen-directed therapy. Treatment options are obviously simplified if the etiologic agent is established or strongly suspected. Antibiotic decisions based on microbial pathogens are summarized in table 14 (C-III).

Empirical antibiotic decisions. The selection of antibiotics in the absence of an etiologic diagnosis (when Gram stains and cultures are not diagnostic) is based on multiple variables, including severity of the illness, the patient's age, antimicrobial intolerance or side effects, clinical features, comorbidities, concomitant medications, exposures, and epidemiological setting (B-II) (tables 7 and 15).

Preferred antimicrobials. The antimicrobial agents preferred for most patients are (in no special order) a macrolide (erythromycin, clarithromycin, or azithromycin; clarithromycin or azithromycin is preferred if *H. influenzae* is suspected), doxycycline, or a fluoroquinolone (levofloxacin, moxifloxacin, gatifloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae*).

Alternative options. Amoxicillin-clavulanate and some second-generation cephalosporins (cefuroxime, cefpodoxime, and cefprozil) are appropriate for infections ascribed to *S. pneumoniae* or *H. influenzae*. These agents are not active against atypical agents. Some authorities prefer macrolides or doxycycline for patients aged <50 years who have no comorbidities and fluoroquinolones for patients who are aged >50 years or have comorbidities.

Management of Patients Who Are Hospitalized

Diagnostic studies. Diagnostic studies recommended for hospitalized patients are summarized in table 5 (B-II). Patients hospitalized for acute pneumonia should have blood cultures performed, preferably of specimens obtained from separate sites ≥10 min apart and before antibiotic administration (B-II). A deep-cough expectorated sputum sample procured by a nurse or physician should be obtained before antibiotic administration (B-II). This sample should be transported to the laboratory for Gram staining and culture within 2 h of collection. Testing for *Legionella* species, *M. tuberculosis,* and other pathogens should be requested when indicated. Antimicrobial treatment should be initiated promptly and should not be delayed by an attempt to obtain pretreatment specimens for microbiological studies from acutely ill patients (B-III). Induced sputum sam-

Table 14. Pathogen-directed antimicrobial therapy for community-acquired pneumonia.

Organism	Preferred antimicrobial	Alternative antimicrobial
Streptococcus pneumoniae		
Penicillin-susceptible[a]	Penicillin G; amoxicillin	Cephalosporins (cefazolin, cefuroxime, cefotaxime, ceftriaxone, or cefepime); oral cephalosporins (cefpodoxime, cefprozil, or cefuroxime); imipenem or meropenem; macrolides[b]; clindamycin; fluoroquinolone[c]; doxycycline; ampicillin ± sulbactam or piperacillin ± tazobactam)
Penicillin-resistant[d]	Agents based on in vitro susceptibility tests, including cefotaxime and ceftriaxone; fluoroquinolone[c]; vancomycin	—
Haemophila influenzae	Cephalosporin (2d or 3d generation); doxycycline; β-lactam/β-lactamase inhibitor; azithromycin; TMP-SMZ	Fluoroquinolone[c]; clarithromycin
Moraxella catarrhalis	Cephalosporin (2d or 3d generation); TMP-SMZ; macrolide; β-lactam/β-lactamase inhibitor	Fluoroquinolone[c]
Anaerobe	β-Lactam/β-lactamase inhibitor; clindamycin	Imipenem
Staphylococcal aureus[e]		
Methicillin-susceptible	Nafcillin/oxacillin ± rifampin or gentamicin[e]	Cefazolin or cefuroxime; vancomycin; clindamycin; TMP-SMZ
Methicillin-resistant	Vancomycin ± rifampin or gentamicin	Linezolid
Enterobacteriaceae[f]	Cephalosporin (3d generation) ± aminoglycoside; carbapenem	Aztreonam; β-lactam/β-lactamase inhibitor; fluoroquinolone[c]
Pseudomonas aeruginosa[e]	Aminoglycoside + antipseudomonal β-lactam: ticarcillin, piperacillin, mezlocillin, ceftazidime, cefepime, aztreonam, or carbapenem	Aminoglycoside + ciprofloxacin; ciprofloxacin + antipseudomonal β-lactam
Legionella	Macrolide[b] ± rifampin; fluoroquinolone[c] (including ciprofloxacin)	Doxycycline ± rifampin
Mycoplasma pneumoniae	Doxycycline; macrolide[b]	Fluoroquinolone[c]
Chlamydia pneumoniae	Doxycycline; macrolide[b]	Fluoroquinolone[c]
Chlamydia psittaci	Doxycycline	Erythromycin; chloramphenicol
Nocardia	TMP-SMZ; sulfonamide ± minocycline or amikacin	Imipenem ± amikacin; doxycycline or minocycline
Coxiella burnetii (Q fever)	Tetracycline	Chloramphenicol
Influenza virus	Amantadine or rimantadine (influenza A); zanamivir or oseltamivir (influenza A or B)	—
Hantavirus	Supportive care	—

NOTE.　TMP-SMZ, trimethoprim-sulfamethoxazole; ±, with or without.

[a] MIC, <2 μg/mL.

[b] Erythromycin, clarithromycin, azithromycin, or dirithromycin; *S. pneumoniae,* especially strains with reduced susceptibility to penicillin, should have verified in vitro susceptibility.

[c] Levofloxacin, gatifloxacin, moxifloxacin, trovafloxacin, or other fluoroquinolone with enhanced activity against *S. pneumoniae;* ciprofloxacin is appropriate for *Legionella, C. pneumoniae,* fluoroquinolone-susceptible *S. aureus,* and most gram-negative bacilli; ciprofloxacin may not be as effective as other quinolones against *S. pneumoniae.*

[d] MIC, ≥2 μg/mL.

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

[f] Coliforms: *Escherichia coli, Klebsiella, Proteus,* and *Enterobacter.*

ples have established value for detection of *P. carinii* and *M. tuberculosis,* and their use generally should be limited to cases with these diagnostic considerations (A-I). Bronchoscopy or bronchoscopy with quantitative bacteriology and other invasive diagnostic techniques should be reserved for selected cases (B-III), such as pneumonia in an immunosuppressed host, suspected tuberculosis in the absence of a productive cough, chronic pneumonia, pneumonia with suspected neoplasm or foreign body, suspected PCP, or conditions that require a lung biopsy (B-II).

Empirical therapy.　Recommendations for empirical treatment of hospitalized patients are different in these guidelines than in the 1998 version [4]. A regimen of treatment with a β-lactam plus a macrolide or monotherapy with a fluoroquinolone is preferred. The rationale for recommending these regimens is based on studies showing that these regimens were associated with a significant reduction in mortality, compared with that associated with administration of cephalosporin alone [189]. Another study supports this observation [190]. Caution is necessary in the interpretation of these studies, since they may reflect temporal or geographic differences. These studies did not have a sufficient number of patients treated only with macrolides to justify conclusions about that category, although recent studies suggest azithromycin monotherapy is equivalent to a β-lactam or a β-lactam plus erythromycin. The recommendation of combination treatment for patients hospitalized in the ICU is based on limited data supporting monotherapy with macrolides or fluoroquinolones for patients who are critically ill with pneumococcal pneumonia.

Recommendations for treating CAP that is sufficiently severe

Table 15. Empirical selection of antimicrobial agents for treating patients with community-acquired pneumonia.

Outpatients
  Generally preferred are (not in any particular order): doxycycline, a macrolide, or a fluoroquinolone
  Selection considerations (see text, Management of Patients Who Do Not Require Hospitalization)
    These agents have activity against the most likely pathogens in this setting, which include *Streptococcus pneumoniae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae*
    Selection should be influenced by regional antibiotic susceptibility patterns for *S. pneumoniae* and the presence of other risk factors for drug-resistant *S. pneumoniae*
    Penicillin-resistant pneumococci may be resistant to macrolides and/or doxycycline
    For older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients
Hospitalized patients
  General medical ward
    Generally preferred are: an extended spectrum cephalosporin combined with a macrolide or a β-lactam/β-lactamase inhibitor combined with a macrolide or a fluoroquinolone (alone)
  Intensive care unit
    Generally preferred are: an extended-spectrum cephalosporin or β-lactam/β-lactamase inhibitor plus either fluoroquinolone or macrolide
    Alternatives or modifying factors (see text, Management of Patients Who Are Hospitalized, Special considerations)
      Structural lung disease: antipseudomonal agents (piperacillin, piperacillin-tazobactam, carbapenem, or cefepime) plus a fluoroquinolone (including high-dose ciprofloxacin)
      β-Lactam allergy: fluoroquinolone ± clindamycin
      Suspected aspiration: fluoroquinolone with or without clindamycin, metronidazole, or a β-lactam/β-lactamase inhibitor

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NOTE. β-Lactam/β-lactamase inhibitor: ampicillin-sulbactam or piperacillin-tazobactam. Extended-spectrum cephalosporin: cefotaxime or ceftriaxone. Fluoroquinolone: gatifloxacin, levofloxacin, moxifloxacin, or other fluoroquinolone with enhanced activity against *S. pneumoniae* (for aspiration pneumonia, some fluoroquinolones show in vitro activity against anaerobic pulmonary pathogens, although there are no clinical studies to verify activity in vivo). Macrolide: azithromycin, clarithromycin, or erythromycin. ±, with or without.

to require hospitalization in the ICU are the use of a β-lactam combined with a fluoroquinolone or a β-lactam combined with a macrolide. The goal is to provide optimal therapy for the 2 most commonly identified causes of lethal pneumonia, *S. pneumoniae* and *Legionella.* Fluoroquinolones alone are not recommended, because most therapeutic trials for these antimicrobial agents (and for macrolides) exclude seriously ill patients; thus, rigorously collected clinical data concerning seriously ill patients are limited.

Preferred antimicrobials. The antimicrobial agents preferred for most patients are as follows (in no special order): in general medical wards, cefotaxime or ceftriaxone plus a macrolide (azithromycin, clarithromycin, or erythromycin) or a fluoroquinolone alone (levofloxacin, gatifloxacin, moxifloxacin, trovafloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae;* fluoroquinolones with in vitro activity against most clinically significant anaerobic pulmonary pathogens include trovafloxacin, moxifloxacin, and gatifloxacin); and, in ICUs, a β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, or piperacillin-tazobactam) plus either a macrolide or a fluoroquinolone.

Special considerations. For structural disease of the lung, such as bronchiectasis or cystic fibrosis, consider use of a regimen that will be active against *Pseudonomas aeruginosa.* For β-lactam allergy, consider a regimen of fluoroquinolone with or without clindamycin. For suspected aspiration, consider a fluoroquinolone with or without a β-lactam/β-lactamase in-

hibitor (ampicillin-sulbactam or piperacillin-tazobactam), metronidazole, or clindamycin (some fluoroquinolones have good in vitro activity against anaerobes and may not require combination with a second antimicrobial agent [see note about fluoroquinolones in previous paragraph]).

Antibiotic Considerations

Antibiotics are the mainstay of treatment for pneumonia. Guidelines for their selection, summarized in tables 14 (B-II) and 15 (B-II), are based largely on clinical experience and/or in vitro activity. Treatment options are simplified if an etiologic diagnosis is established or highly suspect on the basis of results of rapid tests, such as Gram staining or use of other special stains, antigen detection, or amplification techniques (table 14). The selection of antimicrobial agents is based on multiple variables, including severity of illness, the patient's age, ability to tolerate side effects, clinical features, comorbidity, prior exposure, epidemiological setting, and cost (table 7), as well as the prevalence of drug resistance among respiratory tract pathogens. Suggested regimens for consideration for empirical administration to patients hospitalized for acute pneumonia are summarized in table 15, with a distinction between regimens for general use and regimens for patients who require treatment in the ICU (B-II). The following discussion reviews salient issues.

β-Lactams and related agents. All β-lactams exert their an-

tibacterial effects by interfering with synthesis of the peptido-glycan component of the bacterial cell wall. The β-lactams are inactive against *M. pneumoniae* and *C. pneumoniae,* and are ineffective in the treatment of *Legionella.* The antibacterial spectrum of the penicillins varies from narrow-spectrum agents with activity largely limited to gram-positive cocci (penicillin G, penicillin V, and oxacillin) to expanded-spectrum agents with activity against many gram-negative bacilli (piperacillin, ticarcillin, and mezlocillin). Parenteral penicillin G, parenteral cefotaxime, parenteral ceftriaxone, and oral amoxicillin are generally viewed as the β-lactam drugs of choice for treating infections with *S. pneumoniae,* against which penicillin MICs are ≤1.0 μg/mL [108–111]. Alternatives to penicillin are generally preferred for infections that involve *S. pneumoniae* resistant to penicillin (MIC, ≥2 μg/mL), including ampicillin, cefotaxime, and ceftriaxone. Penicillins combined with β-lactamase inhibitors (amoxicillin-clavulanate, ticarcillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam) are active against β-lactamase–producing organisms, such as *H. influenzae,* anaerobes, and *M. catarrhalis*, but these combinations offer no advantage over penicillin G against *S. pneumoniae.* Ticarcillin has less activity than other penicillins against *S. pneumoniae.*

Cephalosporins. These drugs generally show enhanced activity against aerobic gram-negative bacilli as when going from first- to second- to third-generation agents. The antimicrobial agents in this class most active against strains of *S. pneumoniae* are cefotaxime and ceftriaxone [53, 106, 107], and the clinical relevance of in vitro resistance to these drugs for treating pneumonia has been questioned. Cefuroxime is substantially less active in vitro than cefotaxime and ceftriaxone and has been anecdotally associated with treatment failures [191]. Parenteral cephalosporins that should not be used for pneumococcal pneumonia include first-generation agents, such as cefazolin and cephalexin, and third-generation drugs, such as ceftizoxime and ceftazidime. Oral cephalosporins that are preferred on the basis of their in vitro activity against *S. pneumoniae* are cefuroxime, cefpodoxime, and cefprozil. Most second- and third-generation cephalosporins show moderate to good activity against *H. influenzae* and *M. catarrhalis.* 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 against anaerobes in vitro.

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* and *P. aeruginosa,* and virtually all strains of *H. influenzae, M. catarrhalis,* anaerobes, and methicillin-susceptible *S. aureus.* Activity against penicillin-resistant *S. pneumoniae* is generally adequate.

Macrolides. Erythromycin has a limited antimicrobial spectrum of activity and is poorly tolerated because of gastroin-testinal side effects. Newer macrolides that are better tolerated but more expensive include azithromycin and clarithromycin. All 3 appear to be effective for treating pulmonary infections caused by *M. pneumoniae, C. pneumoniae,* and *Legionella.* About 5% of penicillin-resistant *S. pneumoniae* isolates are resistant to macrolides in vitro; this rate is substantially higher for strains with intermediate- or high-level penicillin resistance [43, 107, 111], so caution is necessary with empirical use in suspected cases of pneumococcal pneumonia.

There are 2 mechanisms of macrolide resistance by *S. pneumoniae.* First, the M phenotype, because of an efflux mechanism, is associated with MICs of 2–8 μg/mL and, in theory, may be overcome by high doses; this mechanism is prevalent in the United States. Second, the ERM phenotype, due to ribosomal alterations, is associated with MICs ≥64 μg/mL; this mechanism predominates in Europe. Cases of macrolide failure have been described anecdotally but have been infrequent so far [114]. Macrolides have reasonably good activity against anaerobes, except for fusobacteria. Community-acquired strains of *S. aureus* are usually susceptible to macrolides. Most bacteria are susceptible or resistant to all 3 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 [192, 193].

Of the 3 macrolides, azithromycin is the most active agent in vitro against *Legionella, H. influenzae,* and *M. pneumoniae,* whereas clarithromycin is the most active against *S. pneumoniae* and *C. pneumoniae.* Azithromycin and erythromycin are available for iv administration. A multicenter prospective study of 864 immunocompetent outpatients with CAP showed erythromycin to be cost-effective antimicrobial therapy [194], and a recent trial showed monotherapy with iv azithromycin was equivalent to a regimen of cefuroxime with or without erythromycin for patients hospitalized with CAP [195]. The IDSA panel felt the latter report supported azithromycin for initial empirical treatment, but concern was expressed that most of the participants were not very ill, the comparator arm was not ideal, and in vitro activity of azithromycin against *S. pneumoniae* was suboptimal.

Quinolones. Currently available agents in this class for pulmonary infections are ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, moxifloxacin, gatifloxacin, and trovafloxacin. 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.* Levofloxacin, sparfloxacin, moxifloxacin, gatifloxacin, and trovafloxacin show enhanced in vitro activity against *S. pneumoniae,* including penicillin-resistant strains [49, 107–111], and initial clinical trials show good results [196, 197].

One study showed clinical outcomes with levofloxacin were significantly better than with a cephalosporin regimen for empirical treatment of CAP [196]. Trovafloxacin has been asso-

ciated with excessive rates of hepatotoxicity, so its use is generally restricted to hospitalized patients who lack alternative antibiotic options. Sparfloxacin has high rates of photosensitivity reactions and higher rates of QT-interval prolongation than other fluoroquinolones. Ciprofloxacin is slightly less active in vitro, and there are anecdotal reports of clinical failures for pneumococcal pneumonia; some authorities feel that a dosage of 750 mg twice daily is adequate for empirical use.

Support for the concern about increasing resistance by *S. pneumoniae* is found in reports of increases in the MICs of fluoroquinolones against sequentially collected strains of *S. pneumoniae* in Hong Kong [116], England [117], Ireland [118], and Canada [115]. Ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and trovafloxacin are available for iv administration.

Aminoglycosides.   The aminoglycosides (gentamicin, tobramycin, netilmicin, and amikacin) show a concentration-dependent bactericidal effect that permits a single-daily-dose regimen. These agents are active in vitro against the aerobic and facultative gram-negative bacilli, including *P. aeruginosa.* Some authorities feel aminoglycosides should not be used as single agents for treating gram-negative bacillary pneumonia. Poor clinical results may be due to suboptimal dosing or to possible inactivation of the drug by the acidic environment at the site of infection [198, 199].

Tetracyclines.   There are multiple members of this class, but the one most frequently used in clinical practice today is doxycycline, on the basis of tolerance, convenience of twice-daily dosing, good bioavailability, and low price [200]. Among respiratory tract pathogens, the tetracyclines are active in vitro against the "atypical" organisms, including *M. pneumoniae, C. pneumoniae,* and *Legionella* [196]. *S. pneumoniae* and *H. influenzae* in the past have been quite susceptible to these agents [201, 202], but ~15% of pneumococci are now resistant [49, 107–112, 197, 198].

Vancomycin.   Vancomycin shows universal activity against *S. pneumoniae* [49, 107–112]. It is also active against other gram-positive organisms, including methicillin-resistant *S. aureus.* There is substantial concern about excessive vancomycin use because it promotes the evolution of enterococci that are resistant to vancomycin and of *S. aureus* strains that are only intermediately susceptible. Pneumococcal tolerance of vancomycin has also recently been described, although the clinical relevance of this finding is unknown.

Clindamycin.   Clindamycin exhibits good in vitro activity against gram-positive cocci, including pneumococci that resist macrolides by the efflux pump mechanism and most methicillin-susceptible *S. aureus* [107–112, 200203]. Many authorities consider clindamycin to be the preferred drug for anaerobic pulmonary infections, including aspiration pneumonia and putrid lung abscess [125, 128–131]. It is inactive against *H. influenzae,* atypical etiologic agents, and a varying proportion of erythromycin-resistant *S. aureus.*

TMP-SMZ.   TMP-SMZ is active in vitro against a broad spectrum of gram-positive and gram-negative organisms but has increasingly lost its efficacy against *S. pneumoniae* [49, 107–112]. About 20%–25% of *S. pneumoniae* strains are resistant, and >70% of penicillin-resistant *S. pneumoniae* isolates are not susceptible to TMP-SMZ. TMP-SMZ is active against such diverse pathogens as *Nocardia asteroides, P. carinii,* and *Stenotrophomonas maltophilia.*

Antiviral agents.   Amantadine and rimantadine are inhibitors of hemagglutinin that have established efficacy in treating and preventing influenza A [154]. Relenza and oseltamivir have established efficacy for treatment of influenza A and B and also appear effective for prevention [155–158]. For treatment, all 4 of these drugs must be given within 40–48 h of the onset of influenza symptoms. Therapeutic trials show a mean reduction in the duration of influenza symptoms, including fever of ~1–1.5 days and a substantial reduction in viral shedding. Amantadine and rimantadine are comparably effective in comparative trials; rimantadine is more expensive but has less CNS toxicity. Relenza and oseltamivir are recently FDA-approved neuraminidase inhibitors that appear equally effective, although no trials comparing these drugs with each other or these drugs with amantadine and rimantadine have been reported.

Possible advantages of the neuraminidase inhibitors are the additional activity against influenza B, lack of CNS toxicity, and reduced probability of resistance; disadvantages are the higher price, the somewhat awkward aerosol-delivery device for and possible wheezing with relenza, and gastrointestinal side effects of oseltamivir. The IDSA panel endorses the use of these antiviral agents for treating influenza (B-I). The need to initiate therapy within 40–48 h requires a rapid diagnostic test for influenza detection or empirical treatment based on typical clinical features in an influenza epidemic. The 4 drugs for influenza A appear equally effective; therefore, selection should be based on availability, toxicity, and cost.

Length and Route of Treatment

We are not aware of any controlled trials that have specifically addressed the question of how long pneumonia should be treated. This decision is usually based on the pathogen, response to treatment, comorbid illness, and complications. Until further data are forthcoming, it seems reasonable to treat pneumonia caused by *S. pneumoniae* until the patient has been afebrile for 72 h (C-III). Pneumoniae caused by bacteria that can necrose pulmonary parenchyma (e.g., *S. aureus, P. aeruginosa, Klebsiella,* and anaerobes) should probably be treated for ≥2 weeks. Pneumonia caused by *M. pneumoniae* or *C. pneumoniae* [204–206] 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 very long half-life in tissues [207].

As cost considerations and pressure to treat patients with pneumonia outside the hospital increase, there is rising interest

in the use of oral therapy. For many drugs that are well absorbed from the gut, there is no clear advantage of parenteral therapy. Nevertheless, for most patients admitted to the hospital, common practice is at least to begin therapy with iv drugs. Although no studies verify a superior outcome, this practice is justified by concern for absorption in acutely ill patients.

Changing from iv to oral therapy is associated with a number of economic, health care, and social benefits. It reduces costs of treatment and shortens length of hospital stay. Numerous randomized controlled trials support this practice [19], providing that the patient's condition is improving clinically and is hemodynamically stable, the patient is able to ingest drugs, and the gastrointestinal tract is functioning normally (A-I). In most cases, these conditions are met within 3 days, and oral therapy can be given at that time. Ideally, the drug that was given parenterally or a closely related one is given orally; if no such oral formulation is available, an oral agent with a similar spectrum of activity should be selected on the basis of in vitro or predicted sensitivity patterns of the established or probable pathogen. As a general matter, the IDSA panel endorses use of bioavailable and active oral antimicrobial agents for patients whose medical conditions are stable and who tolerate these drugs (A-III).

Assessment of response to treatment.   The expected response to treatment should take into account the immunologic capacity of the host, the severity of the illness, the pathogen, and the chest radiographic findings. Subjective response is usually noted within 1–3 days of initiation of treatment. Objective parameters include respiratory symptoms (cough, dyspnea), fever, partial pressure of oxygen, peripheral leukocyte count, and findings on serial radiographs. The most carefully documented response is fever or time to defervescence. With pneumococcal pneumonia in young adults, the average duration of fever after treatment is 2.5 days; in bacteremic pneumonia cases, it is 6–7 days; and in elderly patients who are febrile, it also appears to be longer. Patients with *M. pneumoniae* are usually afebrile within 1–2 days after treatment, whereas immunocompetent patients with legionnaires' disease defervesce in an average of 5 days.

Blood cultures in cases of bacteremic pneumonia are usually negative within 24–48 h of treatment. The pathogen is usually also suppressed in respiratory secretions within 24–48 h; the major exceptions are *P. aeruginosa* (or other gram-negative bacilli), 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, except for those with tuberculosis.

Chest radiographic findings usually clear more slowly than clinical findings, and multiple radiographs are generally not required (A-II) [65]. During the first several days of treatment, there is often radiographic progression despite a good clinical response, presumably reflecting continued inflammatory changes, even in the absence of viable bacteria. Follow-up radiography

during hospitalization may be indicated to assess the position of an endotracheal tube, to assess the position of a line, and to exclude pneumothorax after central line placement or to determine reasons for failure to respond, such as pneumothorax, empyema, progression of infiltrate, cavitation, pulmonary edema, or ARDS.

With regard to host factors, age and presence or absence of comorbid illness are important determinants of the rate of resolution. Radiographs of most patients with bacteremic pneumococcal pneumonia who are aged <50 years clear by 4 weeks; however, in older patients, patients with underlying illness (particularly alcoholism or chronic obstructive pulmonary disease), or patients with extensive pneumonia on presentation, the rate of resolution slows considerably, and only 20%–30% may show clearing by 4 weeks [208, 209]. *L. pneumophila* infection may take substantially longer to clear; only 55% of such infections show complete resolution by 12 weeks [205]. Some authorities advocate follow-up radiography at 7–12 weeks after treatment for selected patients who are aged >40 years and/or smokers, to document resolution of infiltrates and to exclude underlying diseases such as neoplasm.

Patients who fail to respond.   When patients fail to respond or their conditions deteriorate after initiation of empirical therapy, a number of possibilities should be considered (figure 3) (C-III).

1. Incorrect diagnosis (not an infection or underlying noninfectious disease with infectious component): noninfectious illnesses that may account for the clinical and radiographic findings include congestive heart failure, pulmonary embolus, atelectasis, sarcoidosis, neoplasms, radiation pneumonitis, pulmonary drug reactions, vasculitis, ARDS, pulmonary hemorrhage, and inflammatory lung disease.

2. Correct diagnosis: if a correct diagnosis has been made, but the patient fails to respond, the physician should consider each of the following 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 [9]. The mortality rate for patients with bacteremic pneumococcal pneumonia caused by penicillin-susceptible strains of *S. pneumoniae* and treated with penicillin has been consistently reported at ⩾20% [121]. The usual explanation is that physiological events, often in the form of cascades, have been set in motion and are not reversed by simply killing the infecting organism. Occasional patients have local lesions that preclude optimal response, such as obstruction by a neoplasm or a foreign body. Empyema is an infrequent but important cause of failure to respond. Other complications include adverse drug reactions, other complications of medical management such as fluid over-
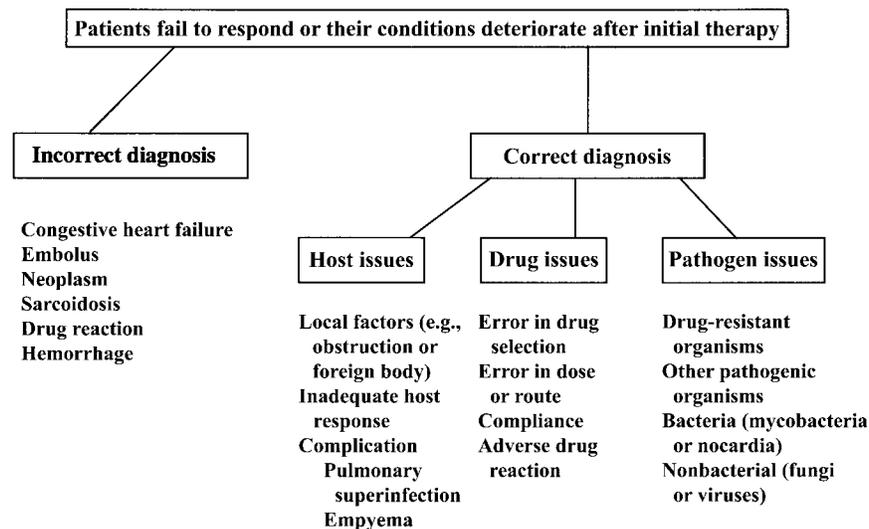
Figure 3. Possible factors to be considered when patients fail to respond or their conditions deteriorate after initiation of empirical therapy

load, pulmonary superinfection or sepsis from an iv line, or any of a host of medical complications related to hospitalization.

(b) Drug-related problem: whether a specific pathogen has been isolated, if a correct etiologic diagnosis of pneumonia has been made, but the patient does not appear to be responding, the physician should always consider the possibility of a medication error, an inappropriate dosing regimen, a problem with compliance, malabsorption, a drug-drug interaction that reduces antimicrobial levels, or other factors that may alter drug delivery to the site of infection. Drug fever or another adverse drug reaction may obscure response to successful therapy.

(c) Pathogen-related problem: the causative organism may have been identified correctly but may be resistant to the antibiotic administered. Examples might include a penicillin-resistant pneumococcus, methicillin-resistant *S. aureus,* or a multiresistant gram-negative-bacillus rod. The wide variety of other pathogens that might not be identified and would not be expected to respond to some or all of the regimens recommended for empirical use include *M. tuberculosis,* fungi, viruses, *Nocardia, C. psittaci,* hantavirus, *C. burnetii,* or *P. carinii.* In some cases, these or other organisms may represent copathogens.

3. Assessment of a nonresponding patient: the assessment of a patient who fails to respond to initial empirical therapy should take into account the possibilities outlined above and in figure 3. Tests appropriate to the individual disease entities should be used to exclude noninfectious possibilities. Specific examples include ventilation-perfusion lung scans and, in selected cases, pulmonary angiography to identify pulmonary embolus, identification of antineutrophil cytoplasmic antibody, and bronchoscopy or open-lung biopsy to diagnose a variety

of noninfectious causes. Some host factors that might influence the range of pathogens, as well as the response, include HIV infection, cystic fibrosis, neoplasms, recent travel, and unusual exposures.

For those 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 during the work up. To rule out an endobronchial lesion or foreign body, bronchoscopy and/or CT scanning 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, CT scanning of the chest may be useful. For pleural effusions detected on chest radiograph, 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 with regard to the nonresponding patient. An aggressive attempt to obtain appropriate expectorated sputum samples may lead to 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 frequent overgrowth by *S. aureus* and gram-negative bacilli. In selected cases, bronchoscopy may be necessary; 1 study suggested that helpful information may be provided by this procedure for up to 41% of patients with CAP whose initial empirical antimicrobial therapy fails [73].

Prevention of CAP

The annual impact of influenza is highly variable. During winters when influenza is epidemic, its impact on CAP is sizable as a result of both primary influenza pneumonia and secondary

bacterial pneumonia. Influenza vaccine is effective in limiting severe disease caused by influenza virus [158] and is recommended to be given annually to persons at increased risk for complications, as well as to health care workers (A-I) [106].

Polyvalent vaccines of pneumococcal capsular polysaccharides have been shown to be effective in preventing pneumococcal pneumonia in American military recruits [210] and in young adult African males [211]. The currently available 23-valent vaccine is ~60% effective in preventing bacteremic pneumococcal infection in immunocompetent adults [212, 213]. Efficacy tends to decline with age and may be unmeasurable in immunocompromised hosts [214, 215]. Despite controversies over efficacy [215–217], the fatality rate of bacteremic pneumococcal infection among those aged >64 years and/or with a variety of underlying systemic illnesses remains high, the potential for benefit in individual cases cannot be denied, and the vaccine is essentially free of serious side effects. Accordingly, the IDSA panel endorses current CDC guidelines for pneumococcal vaccine (B-II). More than half of patients hospitalized with pneumococcal disease have had other hospitalizations within the previous 5 years [218]. Unvaccinated patients with risk factors for pneumococcal disease and influenza should consequently 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 hospital discharge). The vaccines are inexpensive and can be given simultaneously.

Performance Indicators

The following are recommended performance indicators: (1) blood cultures before antibiotic therapy for hospitalized patients (studies indicate that compliance with this recommendation is associated with a significant reduction in mortality [67]); (2) initiation of antibiotic therapy within 8 h of hospitalization (prior studies indicate that compliance with this recommendation is associated with a significant reduction in mortality [183]); (3) use of culture and/or urinary antigen testing for detecting *Legionella* species in 50% of patients hospitalized in the ICU for enigmatic CAP; (4) demonstration of an infiltrate by chest radiography or other imaging technique for all patients with an ICD-9–code diagnosis of CAP who do not have AIDS or neutropenia; and (5) measurement of blood gases or performance of pulse oximetry before admission or within 8 h of admission.

Acknowledgments

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