

# Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

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## EXECUTIVE SUMMARY

Improving the care of adult patients with community-acquired pneumonia (CAP) has been the focus of many different organizations, and several have developed guidelines for management of CAP. Two of the most widely referenced are those of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS). In response to confusion regarding differences between their respective guidelines, the IDSA and the ATS convened a joint committee to develop a unified CAP guideline document.

The guidelines are intended primarily for use by emergency medicine physicians, hospitalists, and primary care practitioners; however, the extensive literature evaluation suggests that they are also an appropriate

starting point for consultation by specialists. Substantial overlap exists among the patients whom these guidelines address and those discussed in the recently published guidelines for health care-associated pneumonia (HCAP). Pneumonia in nonambulatory residents of nursing homes and other long-term care facilities epidemiologically mirrors hospital-acquired pneumonia and should be treated according to the HCAP guidelines. However, certain other patients whose conditions are included in the designation of HCAP are better served by management in accordance with CAP guidelines with concern for specific pathogens.

## Implementation of Guideline Recommendations

1. Locally adapted guidelines should be implemented to improve process of care variables and relevant clinical outcomes. (Strong recommendation; level I evidence.)

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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Enthusiasm for developing these guidelines derives, in large part, from evidence that previous CAP guidelines have led to improvement in clinically relevant outcomes. Consistently beneficial effects in clinically relevant parameters (listed in table 3) followed the introduction of a comprehensive protocol (including a combination of components from table 2) that increased compliance with published guidelines. The first recommendation, therefore, is that CAP management guidelines be locally adapted and implemented.

#### **Documented benefits.**

2. CAP guidelines should address a comprehensive set of elements in the process of care rather than a single element in isolation. (Strong recommendation; level III evidence.)
3. Development of local CAP guidelines should be directed toward improvement in specific and clinically relevant outcomes. (Moderate recommendation; level III evidence.)

#### **Site-of-Care Decisions**

Almost all of the major decisions regarding management of CAP, including diagnostic and treatment issues, revolve around the initial assessment of severity. Site-of-care decisions (e.g., hospital vs. outpatient, intensive care unit [ICU] vs. general ward) are important areas for improvement in CAP management.

#### **Hospital admission decision.**

4. Severity-of-illness scores, such as the CURB-65 criteria (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater), or prognostic models, such as the Pneumonia Severity Index (PSI), can be used to identify patients with CAP who may be candidates for outpatient treatment. (Strong recommendation; level I evidence.)
5. Objective criteria or scores should always be supplemented with physician determination of subjective factors, including the ability to safely and reliably take oral medication and the availability of outpatient support resources. (Strong recommendation; level II evidence.)
6. For patients with CURB-65 scores  $\geq 2$ , more-intensive treatment—that is, hospitalization or, where appropriate and available, intensive in-home health care services—is usually warranted. (Moderate recommendation; level III evidence.)

Physicians often admit patients to the hospital who could be well managed as outpatients and who would generally prefer to be treated as outpatients. Objective scores, such as the CURB-65 score or the PSI, can assist in identifying patients who may be appropriate for outpatient care, but the use of such scores must be tempered by the physician's determination of additional critical factors, including the ability to safely and reliably

take oral medication and the availability of outpatient support resources.

#### **ICU admission decision.**

7. Direct admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation. (Strong recommendation; level II evidence.)
8. Direct admission to an ICU or high-level monitoring unit is recommended for patients with 3 of the minor criteria for severe CAP listed in table 4. (Moderate recommendation; level II evidence.)

In some studies, a significant percentage of patients with CAP are transferred to the ICU in the first 24–48 h after hospitalization. Mortality and morbidity among these patients appears to be greater than those among patients admitted directly to the ICU. Conversely, ICU resources are often overstretched in many institutions, and the admission of patients with CAP who would not directly benefit from ICU care is also problematic. Unfortunately, none of the published criteria for severe CAP adequately distinguishes these patients from those for whom ICU admission is necessary. In the present set of guidelines, a new set of criteria has been developed on the basis of data on individual risks, although the previous ATS criteria format is retained. In addition to the 2 major criteria (need for mechanical ventilation and septic shock), an expanded set of minor criteria (respiratory rate,  $>30$  breaths/min; arterial oxygen pressure/fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) ratio,  $<250$ ; multilobar infiltrates; confusion; blood urea nitrogen level,  $>20$  mg/dL; leukopenia resulting from infection; thrombocytopenia; hypothermia; or hypotension requiring aggressive fluid resuscitation) is proposed (table 4). The presence of at least 3 of these criteria suggests the need for ICU care but will require prospective validation.

#### **Diagnostic Testing**

9. In addition to a constellation of suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data, is required for the diagnosis of pneumonia. (Moderate recommendation; level III evidence.)

#### **Recommended diagnostic tests for etiology.**

10. Patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues. (Strong recommendation; level II evidence.)

Recommendations for diagnostic testing remain controversial. The overall low yield and infrequent positive impact on clinical care argue against the routine use of common tests,

such as blood and sputum cultures. Conversely, these cultures may have a major impact on the care of an individual patient and are important for epidemiologic reasons, including the antibiotic susceptibility patterns used to develop treatment guidelines. A list of clinical indications for more extensive diagnostic testing (table 5) was, therefore, developed, primarily on the basis of 2 criteria: (1) when the result is likely to change individual antibiotic management and (2) when the test is likely to have the highest yield.

11. Routine diagnostic tests to identify an etiologic diagnosis are optional for outpatients with CAP. (Moderate recommendation; level III evidence.)
12. Pretreatment blood samples for culture and an expectorated sputum sample for stain and culture (in patients with a productive cough) should be obtained from hospitalized patients with the clinical indications listed in table 5 but are optional for patients without these conditions. (Moderate recommendation; level I evidence.)
13. Pretreatment Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures for collection, transport, and processing of samples can be met. (Moderate recommendation; level II evidence.)
14. Patients with severe CAP, as defined above, should at least have blood samples drawn for culture, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* performed, and expectorated sputum samples collected for culture. For intubated patients, an endotracheal aspirate sample should be obtained. (Moderate recommendation; level II evidence.)

The most clear-cut indication for extensive diagnostic testing is in the critically ill CAP patient. Such patients should at least have blood drawn for culture and an endotracheal aspirate obtained if they are intubated; consideration should be given to more extensive testing, including urinary antigen tests for *L. pneumophila* and *S. pneumoniae* and Gram stain and culture of expectorated sputum in nonintubated patients. For inpatients without the clinical indications listed in table 5, diagnostic testing is optional (but should not be considered wrong).

### Antibiotic Treatment

**Empirical antimicrobial therapy.** Empirical antibiotic recommendations (table 7) have not changed significantly from those in previous guidelines. Increasing evidence has strengthened the recommendation for combination empirical therapy for severe CAP. Only 1 recently released antibiotic has been added to the recommendations: ertapenem, as an acceptable  $\beta$ -lactam alternative for hospitalized patients with risk factors for infection with gram-negative pathogens other than *Pseudomonas aeruginosa*. At present, the committee is awaiting further evaluation of the safety of telithromycin by the US Food

and Drug Administration before making its final recommendation regarding this drug. Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug. Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.

### Outpatient treatment

15. Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:
  - A. A macrolide (azithromycin, clarithromycin, or erythromycin) (strong recommendation; level I evidence)
  - B. Doxycycline (weak recommendation; level III evidence)
16. Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
  - A. A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
  - B. A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence) (High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-clavulanate [2 g 2 times daily] is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime [500 mg 2 times daily]; doxycycline [level II evidence] is an alternative to the macrolide.)
17. In regions with a high rate (>25%) of infection with high-level (MIC,  $\geq 16$   $\mu\text{g}/\text{mL}$ ) macrolide-resistant *S. pneumoniae*, consider the use of alternative agents listed above in recommendation 16 for any patient, including those without comorbidities. (Moderate recommendation; level III evidence.)

### Inpatient, non-ICU treatment

18. A respiratory fluoroquinolone (strong recommendation; level I evidence)
19. A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence) (Preferred  $\beta$ -lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline [level III evidence] as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients.)

Increasing resistance rates have suggested that empirical therapy with a macrolide alone can be used only for the treat-

ment of carefully selected hospitalized patients with nonsevere disease and without risk factors for infection with drug-resistant pathogens. However, such monotherapy cannot be routinely recommended.

#### Inpatient, ICU treatment

20. A  $\beta$ -lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) or a fluoroquinolone (level I evidence) (strong recommendation) (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)
21. For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal  $\beta$ -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose)  
**or**  
the above  $\beta$ -lactam plus an aminoglycoside and azithromycin  
**or**  
the above  $\beta$ -lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above  $\beta$ -lactam). (Moderate recommendation; level III evidence.)
22. For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid. (Moderate recommendation; level III evidence.)

Infections with the overwhelming majority of CAP pathogens will be adequately treated by use of the recommended empirical regimens. The emergence of methicillin-resistant *S. aureus* as a CAP pathogen and the small but significant incidence of CAP due to *P. aeruginosa* are the exceptions. These pathogens occur in specific epidemiologic patterns and/or with certain clinical presentations, for which empirical antibiotic coverage may be warranted. However, diagnostic tests are likely to be of high yield for these pathogens, allowing early discontinuation of empirical treatment if results are negative. The risk factors are included in the table 5 recommendations for indications for increased diagnostic testing.

#### ***Pathogens suspected on the basis of epidemiologic considerations.***

Risk factors for other uncommon etiologies of CAP are listed in table 8, and recommendations for treatment are included in table 9.

#### ***Pathogen-directed therapy.***

23. Once the etiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen. (Moderate recommendation; level III evidence.)
24. Early treatment (within 48 h of the onset of symptoms)

with oseltamivir or zanamivir is recommended for influenza A. (Strong recommendation; level I evidence.)

25. Use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 h (level I evidence), but these drugs may be used to reduce viral shedding in hospitalized patients or for influenza pneumonia. (Moderate recommendation; level III evidence.)

#### Pandemic influenza

26. Patients with an illness compatible with influenza and with known exposure to poultry in areas with previous H5N1 infection should be tested for H5N1 infection. (Moderate recommendation; level III evidence.)
27. In patients with suspected H5N1 infection, droplet precautions and careful routine infection control measures should be used until an H5N1 infection is ruled out. (Moderate recommendation; level III evidence.)
28. Patients with suspected H5N1 infection should be treated with oseltamivir (level II evidence) and antibacterial agents targeting *S. pneumoniae* and *S. aureus*, the most common causes of secondary bacterial pneumonia in patients with influenza (level III evidence). (Moderate recommendation.)

#### ***Time to first antibiotic dose.***

29. For patients admitted through the emergency department (ED), the first antibiotic dose should be administered while still in the ED. (Moderate recommendation; level III evidence.)

Rather than designating a specific window in which to initiate treatment, the committee felt that hospitalized patients with CAP should receive the first antibiotic dose in the ED.

#### ***Switch from intravenous to oral therapy.***

30. Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract. (Strong recommendation; level II evidence.)
31. Patients should be discharged as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is not necessary. (Moderate recommendation; level II evidence.)

#### ***Duration of antibiotic therapy.***

32. Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy (level II evidence). (Moderate recommendation.)

33. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis. (Weak recommendation; level III evidence.)

#### **Other Treatment Considerations**

34. Patients with CAP who have persistent septic shock despite adequate fluid resuscitation should be considered for treatment with drotrecogin alfa activated within 24 h of admission. (Weak recommendation; level II evidence.)
35. Hypotensive, fluid-resuscitated patients with severe CAP should be screened for occult adrenal insufficiency. (Moderate recommendation; level II evidence.)
36. Patients with hypoxemia or respiratory distress should receive a cautious trial of noninvasive ventilation unless they require immediate intubation because of severe hypoxemia ( $\text{PaO}_2/\text{FiO}_2$  ratio,  $<150$ ) and bilateral alveolar infiltrates. (Moderate recommendation; level I evidence.)
37. Low-tidal-volume ventilation ( $6 \text{ cm}^3/\text{kg}$  of ideal body weight) should be used for patients undergoing ventilation who have diffuse bilateral pneumonia or acute respiratory distress syndrome. (Strong recommendation; level I evidence.)

#### **Management of Nonresponding Pneumonia**

##### **Definitions and classification.**

38. The use of a systematic classification of possible causes of failure to respond, based on time of onset and type of failure (table 11), is recommended. (Moderate recommendation; level II evidence.)

As many as 15% of patients with CAP may not respond appropriately to initial antibiotic therapy. A systematic approach to these patients (table 11) will help to determine the cause. Because determination of the cause of failure is more accurate if the original microbiological etiology is known, risk factors for nonresponse or deterioration (table 12) figure prominently in the list of situations in which more aggressive and/or extensive initial diagnostic testing is warranted (table 5).

##### **Prevention (see table 13)**

39. All persons  $\geq 50$  years of age, others at risk for influenza complications, household contacts of high-risk persons, and health care workers should receive inactivated influenza vaccine as recommended by the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. (Strong recommendation; level I evidence.)
40. The intranasally administered live attenuated vaccine is an alternative vaccine formulation for some persons 5–49

years of age without chronic underlying diseases, including immunodeficiency, asthma, or chronic medical conditions. (Strong recommendation; level I evidence.)

41. Health care workers in inpatient and outpatient settings and long-term care facilities should receive annual influenza immunization. (Strong recommendation; level I evidence.)
42. Pneumococcal polysaccharide vaccine is recommended for persons  $\geq 65$  years of age and for those with selected high-risk concurrent diseases, according to current Advisory Committee on Immunization Practices guidelines. (Strong recommendation; level II evidence.)
43. Vaccination status should be assessed at the time of hospital admission for all patients, especially those with medical illnesses. (Moderate recommendation; level III evidence.)
44. Vaccination may be performed either at hospital discharge or during outpatient treatment. (Moderate recommendation; level III evidence.)
45. Influenza vaccine should be offered to persons at hospital discharge or during outpatient treatment during the fall and winter. (Strong recommendation; level III evidence.)
46. Smoking cessation should be a goal for persons hospitalized with CAP who smoke. (Moderate recommendation; level III evidence.)
47. Smokers who will not quit should also be vaccinated for both pneumococcus and influenza. (Weak recommendation; level III evidence.)
48. Cases of pneumonia that are of public health concern should be reported immediately to the state or local health department. (Strong recommendation; level III evidence.)
49. Respiratory hygiene measures, including the use of hand hygiene and masks or tissues for patients with cough, should be used in outpatient settings and EDs as a means to reduce the spread of respiratory infections. (Strong recommendation; level III evidence.)

#### **INTRODUCTION**

Improving the care of patients with community-acquired pneumonia (CAP) has been the focus of many different organizations. Such efforts at improvement in care are warranted, because CAP, together with influenza, remains the seventh leading cause of death in the United States [1]. According to one estimate, 915,900 episodes of CAP occur in adults  $\geq 65$  years of age each year in the United States [2]. Despite advances in antimicrobial therapy, rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available [3].

Groups interested in approaches to the management of CAP include professional societies, such as the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA); government agencies or their contract agents, such as

the Center for Medicare and Medicaid Services and the Department of Veterans Affairs; and voluntary accrediting agencies, such as the Joint Commission on Accreditation of Healthcare Organizations. In addition, external review groups and consumer groups have chosen CAP outcomes as major quality indicators. Such interest has resulted in numerous guidelines for the management of CAP [4]. Some of these guidelines represent truly different perspectives, including differences in health care systems, in the availability of diagnostic tools or therapeutic agents, or in either the etiology or the antibiotic susceptibility of common causative microorganisms. The most widely referenced guidelines in the United States have been those published by the ATS [5, 6] and the IDSA [7–9].

Differences, both real and imagined, between the ATS and IDSA guidelines have led to confusion for individual physicians, as well as for other groups who use these published guidelines rather than promulgating their own. In response to this concern, the IDSA and the ATS convened a joint committee to develop a unified CAP guideline document. This document represents a consensus of members of both societies, and both governing councils have approved the statement.

**Purpose and scope.** The purpose of this document is to update clinicians with regard to important advances and controversies in the management of patients with CAP. The committee chose not to address CAP occurring in immunocompromised patients, including solid organ, bone marrow, or stem cell transplant recipients; patients receiving cancer chemotherapy or long-term (>30 days) high-dose corticosteroid treatment; and patients with congenital or acquired immunodeficiency or those infected with HIV who have CD4 cell counts <350 cells/mm<sup>3</sup>, although many of these patients may be infected with the same microorganisms. Pneumonia in children (≤18 years of age) is also not addressed.

Substantial overlap exists among the patients these guidelines address and those discussed in the recently published guidelines for health care–associated pneumonia (HCAP) [10]. Two issues are pertinent: (1) an increased risk of infection with drug-resistant isolates of usual CAP pathogens, such as *Streptococcus pneumoniae*, and (2) an increased risk of infection with less common, usually hospital-associated pathogens, such as *Pseudomonas* and *Acinetobacter* species and methicillin-resistant *Staphylococcus aureus* (MRSA). Pneumonia in nonambulatory residents of nursing homes and other long-term care facilities epidemiologically mirrors hospital-acquired pneumonia and should be treated according to the HCAP guidelines. However, certain other patients whose conditions are included under the designation of HCAP are better served by management in accordance with CAP guidelines with concern for specific pathogens. For example, long-term dialysis alone is a risk for MRSA infection but does not necessarily predispose patients to infection with other HCAP pathogens, such as *Pseudomonas aeru-*

*ginosa* or *Acinetobacter* species. On the other hand, certain patients with chronic obstructive pulmonary disease (COPD) are at greater risk for infection with *Pseudomonas* species but not MRSA. These issues will be discussed in specific sections below.

The committee started with the premise that mortality due to CAP can be decreased. We, therefore, have placed the greatest emphasis on aspects of the guidelines that have been associated with decreases in mortality. For this reason, the document focuses mainly on management and minimizes discussions of such factors as pathophysiology, pathogenesis, mechanisms of antibiotic resistance, and virulence factors.

The committee recognizes that the majority of patients with CAP are cared for by primary care, hospitalist, and emergency medicine physicians [11], and these guidelines are, therefore, directed primarily at them. The committee consisted of infectious diseases, pulmonary, and critical care physicians with interest and expertise in pulmonary infections. The expertise of the committee and the extensive literature evaluation suggest that these guidelines are also an appropriate starting point for consultation by these types of physicians.

Although much of the literature cited originates in Europe, these guidelines are oriented toward the United States and Canada. Although the guidelines are generally applicable to other parts of the world, local antibiotic resistance patterns, drug availability, and variations in health care systems suggest that modification of these guidelines is prudent for local use.

**Methodology.** The process of guideline development started with the selection of committee cochairs by the presidents of the IDSA [12] and ATS [13], in consultation with other leaders in the respective societies. The committee cochairs were charged with selection of the rest of the committee. The IDSA members were those involved in the development of previous IDSA CAP guidelines [9], whereas ATS members were chosen in consultation with the leadership of the Mycobacteria Tuberculosis and Pulmonary Infection Assembly, with input from the chairs of the Clinical Pulmonary and Critical Care assemblies. Committee members were chosen to represent differing expertise and viewpoints on the various topics. One acknowledged weakness of this document is the lack of representation by primary care, hospitalist, and emergency medicine physicians.

The cochairs generated a general outline of the topics to be covered that was then circulated to committee members for input. A conference phone call was used to review topics and to discuss evidence grading and the general aims and expectations of the document. The topics were divided, and committee members were assigned by the cochairs and charged with presentation of their topic at an initial face-to-face meeting, as well as with development of a preliminary document dealing with their topic. Controversial topics were assigned to 2 committee members, 1 from each society.

An initial face-to-face meeting of a majority of committee members involved presentations of the most controversial topics, including admission decisions, diagnostic strategies, and antibiotic therapy. Prolonged discussions followed each presentation, with consensus regarding the major issues achieved before moving to the next topic. With input from the rest of the committee, each presenter and committee member assigned to the less controversial topics prepared an initial draft of their section, including grading of the evidence. Iterative drafts of the statement were developed and distributed by e-mail for critique, followed by multiple revisions by the primary authors. A second face-to-face meeting was also held for discussion of the less controversial areas and further critique of the initial drafts. Once general agreement on the separate topics was obtained, the coauthors incorporated the separate documents into a single statement, with substantial editing for style and consistency. The document was then redistributed to committee members to review and update with new information from the literature up to June 2006. Recommended changes were reviewed by all committee members by e-mail and/or conference phone call and were incorporated into the final document by the coauthors.

This document was then submitted to the societies for approval. Each society independently selected reviewers, and changes recommended by the reviewers were discussed by the committee and incorporated into the final document. The guideline was then submitted to the IDSA Governing Council and the ATS Board of Directors for final approval.

**Grading of guideline recommendations.** Initially, the committee decided to grade only the strength of the evidence, using a 3-tier scale (table 1) used in a recent guideline from both societies [10]. In response to reviewers' comments and the maturation of the field of guideline development [14], a separate grading of the strength of the recommendations was added to the final draft. More extensive and validated criteria, such as GRADE [14], were impractical for use at this stage. The 3-tier scale similar to that used in other IDSA guideline documents [12] and familiar to many of the committee members was therefore chosen.

The strength of each recommendation was graded as "strong," "moderate," or "weak." Each committee member independently graded each recommendation on the basis of not only the evidence but also expert interpretation and clinical applicability. The final grading of each recommendation was a composite of the individual committee members' grades. For the final document, a strong recommendation required  $\geq 6$  (of 12) of the members to consider it to be strong and the majority of the others to grade it as moderate.

The implication of a strong recommendation is that most patients should receive that intervention. Significant variability in the management of patients with CAP is well documented.

**Table 1. Levels of evidence.**

Evidence level	Definition
Level I (high)	Evidence from well-conducted, randomized controlled trials.
Level II (moderate)	Evidence from well-designed, controlled trials without randomization (including cohort, patient series, and case-control studies). Level II studies also include any large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of data on new therapies that were not collected in a randomized fashion.
Level III (low)	Evidence from case studies and expert opinion. In some instances, therapy recommendations come from antibiotic susceptibility data without clinical observations.

Some who use guidelines suggest that this variability itself is undesirable. Industrial models suggesting that variability per se is undesirable may not always be relevant to medicine [15]. Such models do not account for substantial variability among patients, nor do they account for variable end points, such as limitation of care in patients with end-stage underlying diseases who present with CAP. For this reason, the committee members feel strongly that 100% compliance with guidelines is not the desired goal. However, the rationale for variation from a strongly recommended guideline should be apparent from the medical record.

Conversely, moderate or weak recommendations suggest that, even if a majority would follow the recommended management, many practitioners may not. Deviation from guidelines may occur for a variety of reasons [16, 17]. One document cannot cover all of the variable settings, unique hosts, or epidemiologic patterns that may dictate alternative management strategies, and physician judgment should always supersede guidelines. This is borne out by the finding that deviation from guidelines is greatest in the treatment of patients with CAP admitted to the ICU [18]. In addition, few of the recommendations have level I evidence to support them, and most are, therefore, legitimate topics for future research. Subsequent publication of studies documenting that care that deviates from guidelines results in better outcomes will stimulate revision of the guidelines. The committee anticipates that this will occur, and, for this reason, both the ATS and IDSA leaderships have committed to the revision of these guidelines on a regular basis.

We recognize that these guidelines may be used as a measure of quality of care for hospitals and individual practitioners. Although these guidelines are evidence based, the committee strongly urges that deviations from them not necessarily be

considered substandard care, unless they are accompanied by evidence for worse outcomes in a studied population.

## IMPLEMENTATION OF GUIDELINE RECOMMENDATIONS

1. Locally adapted guidelines should be implemented to improve process of care variables and relevant clinical outcomes. (Strong recommendation; level I evidence.)

Enthusiasm for developing this set of CAP guidelines derives, in large part, from evidence that previous CAP guidelines have led to improvement in clinically relevant outcomes [17, 19–21]. Protocol design varies among studies, and the preferable randomized, parallel group design has been used in only a small minority. Confirmatory studies that use randomized, parallel groups with precisely defined treatments are still needed, but a consistent pattern of benefit is found in the other types of level I studies.

**Documented benefits.** Published protocols have varied in primary focus and comprehensiveness, and the corresponding benefits vary from one study to another. However, the most impressive aspect of this literature is the consistently beneficial effect seen in some clinically relevant parameter after the introduction of a protocol that increases compliance with published guidelines.

A decrease in mortality with the introduction of guideline-based protocols was found in several studies [19, 21]. A 5-year study of 28,700 patients with pneumonia who were admitted during implementation of a pneumonia guideline demonstrated that the crude 30-day mortality rate was 3.2% lower with the guideline (adjusted OR, 0.69; 95% CI, 0.49–0.97) [19], compared with that among patients treated concurrently by nonaffiliated physicians. After implementation of a practice guideline at one Spanish hospital [21], the survival rate at 30 days was higher (OR, 2.14; 95% CI, 1.23–3.72) than at baseline and in comparison with 4 other hospitals without overt protocols. Lower mortality was seen in other studies, although the differences were not statistically significant [22, 23]. Studies that documented lower mortality emphasized increasing the number of patients receiving guideline-recommended antibiotics, confirming results of the multivariate analysis of a retrospective review [24].

When the focus of a guideline was hospitalization, the number of less ill patients admitted to the hospital was consistently found to be lower. Using admission decision support, a prospective study of >1700 emergency department (ED) visits in 19 hospitals randomized between pathway and “conventional” management found that admission rates among low-risk patients at pathway hospitals decreased (from 49% to 31% of patients in Pneumonia Severity Index [PSI] classes I–III;  $P <$

.01) without differences in patient satisfaction scores or rate of readmission [20]. Calculating the PSI score and assigning the risk class, providing oral clarithromycin, and home nursing follow-up significantly ( $P = .01$ ) decreased the number of low-mortality-risk admissions [25]. However, patient satisfaction among outpatients was lower after implementation of this guideline, despite survey data that suggested most patients would prefer outpatient treatment [26]. Of patients discharged from the ED, 9% required hospitalization within 30 days, although another study showed lower readmission rates with the use of a protocol [23]. Admission decision support derived from the 1993 ATS guideline [5] recommendations, combined with outpatient antibiotic recommendations, reduced the CAP hospitalization rate from 13.6% to 6.4% [23], and admission rates for other diagnoses were unchanged. Not surprisingly, the resultant overall cost of care decreased by half ( $P = .01$ ).

Protocols using guidelines to decrease the duration of hospitalization have also been successful. Guideline implementation in 31 Connecticut hospitals decreased the mean length of hospital stay (LOS) from 7 to 5 days ( $P < .001$ ) [27]. An ED-based protocol decreased the mean LOS from 9.7 to 6.4 days ( $P < .0001$ ), with the benefits of guideline implementation maintained 3 years after the initial study [22]. A 7-site trial, randomized by physician group, of guideline alone versus the same guideline with a multifaceted implementation strategy found that addition of an implementation strategy was associated with decreased duration of intravenous antibiotic therapy and LOS, although neither decrease was statistically significant [28]. Several other studies used guidelines to significantly shorten the LOS, by an average of >1.5 days [20, 21].

Markers of process of care can also change with the use of a protocol. The time to first antibiotic dose has been effectively decreased with CAP protocols [22, 27, 29]. A randomized, parallel group study introduced a pneumonia guideline in 20 of 36 small Oklahoma hospitals [29], with the identical protocol implemented in the remaining hospitals in a second phase. Serial measurement of key process measures showed significant improvement in time to first antibiotic dose and other variables, first in the initial 20 hospitals and later in the remaining 16 hospitals. Implementing a guideline in the ED halved the time to initial antibiotic dose [22].

2. CAP guidelines should address a comprehensive set of elements in the process of care rather than a single element in isolation. (Strong recommendation; level III evidence.)

Common to all of the studies documented above, a comprehensive protocol was developed and implemented, rather than one addressing a single aspect of CAP care. No study has documented that simply changing 1 metric, such as time to first antibiotic dose, is associated with a decrease in mortality.

**Table 2. Elements important for local community-acquired pneumonia guidelines.**

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All patients
Initiation of antibiotic therapy at site of diagnosis for hospitalized patients
Antibiotic selection
Empirical
Specific
Admission decision support
Assessment of oxygenation
Intensive care unit admission support
Smoking cessation
Influenza and pneumococcal vaccine administration
Follow-up evaluation
Inpatients only
Diagnostic studies
Timing
Types of studies
Prophylaxis against thromboembolic disease
Early mobilization
Thoracentesis for patients with significant parapneumonic effusions
Discharge decision support
Patient education

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Elements important in CAP guidelines are listed in table 2. Of these, rapid and appropriate empirical antibiotic therapy is consistently associated with improved outcome. We have also included elements of good care for general medical inpatients, such as early mobilization [30] and prophylaxis against thromboembolic disease [31]. Although local guidelines need not include all elements, a logical constellation of elements should be addressed.

- Development of local CAP guidelines should be directed toward improvement in specific and clinically relevant outcomes. (Moderate recommendation; level III evidence.)

In instituting CAP protocol guidelines, the outcomes most relevant to the individual center or medical system should be addressed first. Unless a desire to change clinically relevant outcomes exists, adherence to guidelines will be low, and institutional resources committed to implement the guideline are likely to be insufficient. Guidelines for the treatment of pneumonia must use approaches that differ from current practice and must be successfully implemented before process of care and outcomes can change. For example, Rhew et al. [32] designed a guideline to decrease LOS that was unlikely to change care, because the recommended median LOS was longer than the existing LOS for CAP at the study hospitals. The difficulty in implementing guidelines and changing physician behavior has also been documented [28, 33].

Clinically relevant outcome parameters should be evaluated to measure the effect of the local guideline. Outcome parameters that can be used to measure the effect of implementation of a CAP guideline within an organization are listed in table 3. Just as it is important not to focus on one aspect of care, studying more than one outcome is also important. Improvements in one area may be offset by worsening in a related area; for example, decreasing admission of low-acuity patients might increase the number of return visits to the ED or hospital readmissions [25].

### SITE-OF-CARE DECISIONS

Almost all of the major decisions regarding management of CAP, including diagnostic and treatment issues, revolve around the initial assessment of severity. We have, therefore, organized the guidelines to address this issue first.

**Hospital admission decision.** The initial management decision after diagnosis is to determine the site of care—outpatient, hospitalization in a medical ward, or admission to an ICU. The decision to admit the patient is the most costly issue in the management of CAP, because the cost of inpatient care for pneumonia is up to 25 times greater than that of outpatient care [34] and consumes the majority of the estimated \$8.4–\$10 billion spent yearly on treatment.

Other reasons for avoiding unnecessary admissions are that patients at low risk for death who are treated in the outpatient setting are able to resume normal activity sooner than those who are hospitalized, and 80% are reported to prefer outpatient therapy [26, 35]. Hospitalization also increases the risk of thromboembolic events and superinfection by more-virulent or resistant hospital bacteria [36].

- Severity-of-illness scores, such as the CURB-65 criteria (c<sub>on</sub>fusion, uremia, respiratory rate, low blood pressure, age 65)

**Table 3. Clinically relevant outcome parameters in community-acquired pneumonia.**

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Mortality
Rate of hospital admission
Rate of intensive care unit admission
Delayed transfer to the intensive care unit
Treatment failure
Drug toxicity and adverse effects
Antibiotic resistance in common pathogens
Length of stay
Thirty-day readmission rate
Unscheduled return to emergency department or primary physician office
Return to work/school/normal activities
Patient satisfaction
Cost of care

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years or greater), or prognostic models, such as the PSI, can be used to identify patients with CAP who may be candidates for outpatient treatment. (Strong recommendation; level I evidence.)

Significant variation in admission rates among hospitals and among individual physicians is well documented. Physicians often overestimate severity and hospitalize a significant number of patients at low risk for death [20, 37, 38]. Because of these issues, interest in objective site-of-care criteria has led to attempts by a number of groups to develop such criteria [39–48]. The relative merits and limitations of various proposed criteria have been carefully evaluated [49]. The 2 most interesting are the PSI [42] and the British Thoracic Society (BTS) criteria [39, 45].

The PSI is based on derivation and validation cohorts of 14,199 and 38,039 hospitalized patients with CAP, respectively, plus an additional 2287 combined inpatients and outpatients [42]. The PSI stratifies patients into 5 mortality risk classes, and its ability to predict mortality has been confirmed in multiple subsequent studies. On the basis of associated mortality rates, it has been suggested that risk class I and II patients should be treated as outpatients, risk class III patients should be treated in an observation unit or with a short hospitalization, and risk class IV and V patients should be treated as inpatients [42].

Yealy et al. [50] conducted a cluster-randomized trial of low-, moderate-, and high-intensity processes of guideline implementation in 32 EDs in the United States. Their guideline used the PSI for admission decision support and included recommendations for antibiotic therapy, timing of first antibiotic dose, measurement of oxygen saturation, and blood cultures for admitted patients. EDs with moderate- to high-intensity guideline implementation demonstrated more outpatient treatment of low-risk patients and higher compliance with antibiotic recommendations. No differences were found in mortality rate, rate of hospitalization, median time to return to work or usual activities, or patient satisfaction. This study differs from those reporting a mortality rate difference [19, 21] in that many hospitalized patients with pneumonia were not included. In addition, EDs with low-intensity guideline implementation formed the comparison group, rather than EDs practicing non-guideline, usual pneumonia care.

The BTS original criteria of 1987 have subsequently been modified [39, 51]. In the initial study, risk of death was increased 21-fold if a patient, at the time of admission, had at least 2 of the following 3 conditions: tachypnea, diastolic hypotension, and an elevated blood urea nitrogen (BUN) level. These criteria appear to function well except among patients with underlying renal insufficiency and among elderly patients [52, 53].

The most recent modification of the BTS criteria includes 5

easily measurable factors [45]. Multivariate analysis of 1068 patients identified the following factors as indicators of increased mortality: confusion (based on a specific mental test or disorientation to person, place, or time), BUN level  $>7$  mmol/L (20 mg/dL), respiratory rate  $\geq 30$  breaths/min, low blood pressure (systolic,  $<90$  mm Hg; or diastolic,  $\leq 60$  mm Hg), and age  $\geq 65$  years; this gave rise to the acronym CURB-65. In the derivation and validation cohorts, the 30-day mortality among patients with 0, 1, or 2 factors was 0.7%, 2.1%, and 9.2%, respectively. Mortality was higher when 3, 4, or 5 factors were present and was reported as 14.5%, 40%, and 57%, respectively. The authors suggested that patients with a CURB-65 score of 0–1 be treated as outpatients, that those with a score of 2 be admitted to the wards, and that patients with a score of  $\geq 3$  often required ICU care. A simplified version (CRB-65), which does not require testing for BUN level, may be appropriate for decision making in a primary care practitioner's office [54].

The use of objective admission criteria clearly can decrease the number of patients hospitalized with CAP [20, 23, 25, 55]. Whether the PSI or the CURB-65 score is superior is unclear, because no randomized trials of alternative admission criteria exist. When compared in the same population, the PSI classified a slightly larger percentage of patients with CAP in the low-risk categories, compared with the CURB or CURB-65 criteria, while remaining associated with a similar low mortality rate among patients categorized as low risk [56]. Several factors are important in this comparison. The PSI includes 20 different variables and, therefore, relies on the availability of scoring sheets, limiting its practicality in a busy ED [55]. In contrast, the CURB-65 criteria are easily remembered. However, CURB-65 has not been as extensively studied as the PSI, especially with prospective validation in other patient populations (e.g., the indigent inner-city population), and has not been specifically studied as a means of reducing hospital admission rates. In EDs with sufficient decision support resources (either human or computerized), the benefit of greater experience with the PSI score may favor its use for screening patients who may be candidates for outpatient management [50, 57–59].

5. Objective criteria or scores should always be supplemented with physician determination of subjective factors, including the ability to safely and reliably take oral medication and the availability of outpatient support resources. (Strong recommendation; level II evidence.)

Studies show that certain patients with low PSI or CURB-65 scores [20, 60, 61] require hospital admission, even to the ICU [49, 62, 63]. Both scores depend on certain assumptions. One is that the main rationale for admission of a patient with CAP is risk of death. This assumption is clearly not valid in

all cases. Another is that the laboratory and vital signs used for scoring are stable over time rather than indicative of transient abnormalities. This is also not true in all cases. Therefore, dynamic assessment over several hours of observation may be more accurate than a score derived at a single point in time. Although advantageous to making decisions regarding hospital admission, sole reliance on a score for the hospital admission decision is unsafe.

Reasons for the admission of low-mortality-risk patients fall into 4 categories: (1) complications of the pneumonia itself, (2) exacerbation of underlying diseases(s), (3) inability to reliably take oral medications or receive outpatient care, and/or (4) multiple risk factors falling just above or below thresholds for the score [62]. Use of the PSI score in clinical trials has demonstrated some of its limitations, which may be equally applicable to other scoring techniques. A modification of the original PSI score was needed when it was applied to the admission decision. An arterial saturation of <90% or an arterial oxygen pressure (PaO<sub>2</sub>) of <60 mm Hg as a complication of the pneumonia, was added as a sole indicator for admission for patients in risk classes I–III as an added “margin of safety” in one trial [42]. In addition to patients who required hospital admission because of hypoxemia, a subsequent study identified patients in low PSI risk classes (I–III) who needed hospital admission because of shock, decompensated coexisting illnesses, pleural effusion, inability to maintain oral intake, social problems (the patient was dependent or no caregiver was available), and lack of response to previous adequate empirical antibiotic therapy [64]. Of 178 patients in low PSI risk classes who were treated as inpatients, 106 (60%) presented with at least 1 of these factors. Other medical or psychosocial needs requiring hospital care include intractable vomiting, injection drug abuse, severe psychiatric illness, homelessness, poor overall functional status [65], and cognitive dysfunction [61, 66].

The PSI score is based on a history of diseases that increase risk of death, whereas the CURB-65 score does not directly address underlying disease. However, pneumonia may exacerbate an underlying disease, such as obstructive lung disease, congestive heart failure, or diabetes mellitus, which, by themselves, may require hospital admission [60, 67]. Atlas et al. [25] were able to reduce hospital admissions among patients in PSI risk classes I–III from 58% in a retrospective control group to 43% in a PSI-based intervention group. Ten of 94 patients in the latter group (compared with 0 patients in the control population) were subsequently admitted, several for reasons unrelated to their pneumonia. Also, the presence of rare illnesses, such as neuromuscular or sickle cell disease, may require hospitalization but not affect the PSI score.

The necessary reliance on dichotomous predictor variables (abnormal vs. normal) in most criteria and the heavy reliance on age as a surrogate in the PSI score may oversimplify their

use for admission decisions. For example, a previously healthy 25-year-old patient with severe hypotension and tachycardia and no additional pertinent prognostic factors would be placed in risk class II, whereas a 70-year-old man with a history of localized prostate cancer diagnosed 10 months earlier and no other problems would be placed in risk class IV [42]. Finally, patient satisfaction was lower among patients treated outside the hospital in one study with a PSI-based intervention group [25], suggesting that the savings resulting from use of the PSI may be overestimated and that physicians should consider additional factors not measured by the PSI.

6. For patients with CURB-65 scores  $\geq 2$ , more-intensive treatment—that is, hospitalization or, where appropriate and available, intensive in-home health care services—is usually warranted. (Moderate recommendation; level III evidence.)

Although the PSI and CURB-65 criteria are valuable aids in avoiding inappropriate admissions of low-mortality-risk patients, another important role of these criteria may be to help identify patients at high risk who would benefit from hospitalization. The committee preferred the CURB-65 criteria because of ease of use and because they were designed to measure illness severity more than the likelihood of mortality. Patients with a CURB-65 score  $\geq 2$  are not only at increased risk of death but also are likely to have clinically important physiologic derangements requiring active intervention. These patients should usually be considered for hospitalization or for aggressive in-home care, where available. In a cohort of ~3000 patients, the mortality with a CURB-65 score of 0 was only 1.2%, whereas 3–4 points were associated with 31% mortality [45].

Because the PSI score is not based as directly on severity of illness as are the CURB-65 criteria, a threshold for patients who would require hospital admission or intensive outpatient treatment is harder to define. The higher the score, the greater the need for hospitalization. However, even a patient who meets criteria for risk class V on the basis of very old age and multiple stable chronic illnesses may be successfully managed as an outpatient [23].

#### ***ICU admission decision.***

7. Direct admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation. (Strong recommendation; level II evidence.)
8. Direct admission to an ICU or high-level monitoring unit is recommended for patients with 3 of the minor criteria for severe CAP listed in table 4. (Moderate recommendation; level II evidence.)

The second-level admission decision is whether to place the

**Table 4. Criteria for severe community-acquired pneumonia.**Minor criteria<sup>a</sup>

- Respiratory rate<sup>b</sup>  $\geq 30$  breaths/min
- PaO<sub>2</sub>/FiO<sub>2</sub> ratio<sup>b</sup>  $\leq 250$
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level,  $\geq 20$  mg/dL)
- Leukopenia<sup>c</sup> (WBC count,  $< 4000$  cells/mm<sup>3</sup>)
- Thrombocytopenia (platelet count,  $< 100,000$  cells/mm<sup>3</sup>)
- Hypothermia (core temperature,  $< 36^\circ\text{C}$ )
- Hypotension requiring aggressive fluid resuscitation

## Major criteria

- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

**NOTE.** BUN, blood urea nitrogen; PaO<sub>2</sub>/FiO<sub>2</sub>, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

<sup>a</sup> Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

<sup>b</sup> A need for noninvasive ventilation can substitute for a respiratory rate  $> 30$  breaths/min or a PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $< 250$ .

<sup>c</sup> As a result of infection alone.

patient in the ICU or a high-level monitoring unit rather than on a general medical floor. Approximately 10% of hospitalized patients with CAP require ICU admission [68–70], but the indications vary strikingly among patients, physicians, hospitals, and different health care systems. Some of the variability among institutions results from the availability of high-level monitoring or intermediate care units appropriate for patients at increased risk of complications. Because respiratory failure is the major reason for delayed transfer to the ICU, simple cardiac monitoring units would not meet the criteria for a high-level monitoring unit for patients with severe CAP. One of the most important determinants of the need for ICU care is the presence of chronic comorbid conditions [68–72]. However, approximately one-third of patients with severe CAP were previously healthy [73].

The rationale for specifically defining severe CAP is 4-fold:

- Appropriate placement of patients optimizes use of limited ICU resources.
- Transfer to the ICU for delayed respiratory failure or delayed onset of septic shock is associated with increased mortality [74]. Although low-acuity ICU admissions do occur, the major concern is initial admission to the general medical unit, with subsequent transfer to the ICU. As many as 45% of patients with CAP who ultimately require ICU admission were initially admitted to a non-ICU setting [75]. Many delayed transfers to the ICU represent rapidly progressive pneumonia that is not obvious on admission. However, some have subtle findings, including those included in the minor criteria in table 4, which might warrant direct admission to the ICU.

- The distribution of microbial etiologies differs from that of CAP in general [76–79], with significant implications for diagnostic testing and empirical antibiotic choices. Avoidance of inappropriate antibiotic therapy has also been associated with lower mortality [80, 81].
- Patients with CAP appropriate for immunomodulatory treatment must be identified. The systemic inflammatory response/severe sepsis criteria typically used for generic sepsis trials may not be adequate when applied specifically to severe CAP [82]. For example, patients with unilateral lobar pneumonia may have hypoxemia severe enough to meet criteria for acute lung injury but not have a systemic response.

Several criteria have been proposed to define severe CAP. Most case series have defined it simply as CAP that necessitates ICU admission. Objective criteria to identify patients for ICU admission include the initial ATS definition of severe CAP [5] and its subsequent modification [6, 82], the CURB criteria [39, 45], and PSI severity class V (or IV and V) [42]. However, none of these criteria has been prospectively validated for the ICU admission decision. Recently, these criteria were retrospectively evaluated in a cohort of patients with CAP admitted to the ICU [63]. All were found to be both overly sensitive and nonspecific in comparison with the original clinical decision to admit to the ICU. Revisions of the criteria or alternative criteria were, therefore, recommended.

For the revised criteria, the structure of the modified ATS criteria for severe CAP was retained [6]. The 2 major criteria—mechanical ventilation with endotracheal intubation and septic shock requiring vasopressors—are absolute indications for admission to an ICU.

In contrast, the need for ICU admission is less straightforward for patients who do not meet the major criteria. On the basis of the published operating characteristics of the criteria, no single set of minor criteria is adequate to define severe CAP. Both the ATS minor criteria [75] and the CURB criteria [45] have validity when predicting which patients will be at increased risk of death. Therefore, the ATS minor criteria and the CURB variables were included in the new proposed minor criteria (table 4). Age, by itself, was not felt to be an appropriate factor for the ICU admission decision, but the remainder of the CURB-65 criteria [45] were retained as minor criteria (with the exception of hypotension requiring vasopressors as a major criterion). Rather than the complex criteria for confusion in the original CURB studies, the definition of confusion should be new-onset disorientation to person, place, or time.

Three additional minor criteria were added. Leukopenia (white blood cell count,  $< 4000$  cells/mm<sup>3</sup>) resulting from CAP has consistently been associated with excess mortality, as well as with an increased risk of complications such as acute respiratory distress syndrome (ARDS) [77, 79, 83–87]. In addi-

tion, leukopenia is seen not only in bacteremic pneumococcal disease but also in gram-negative CAP [88, 89]. When leukopenia occurs in patients with a history of alcohol abuse, the adverse manifestations of septic shock and ARDS may be delayed or masked. Therefore, these patients were thought to benefit from ICU monitoring. The coagulation system is often activated in CAP, and development of thrombocytopenia (platelet count,  $<100,000$  cells/mm<sup>3</sup>) is also associated with a worse prognosis [86, 90–92]. Nonexposure hypothermia (core temperature,  $<36^{\circ}\text{C}$ ) also carries an ominous prognosis in CAP [83, 93]. The committee felt that there was sufficient justification for including these additional factors as minor criteria.

Other factors associated with increased mortality due to CAP were also considered, including acute alcohol ingestion and delirium tremens [79, 85, 94], hypoglycemia and hyperglycemia, occult metabolic acidosis or elevated lactate levels [91], and hyponatremia [95]. However, many of these criteria overlap with those selected. Future studies validating the proposed criteria should record these factors as well, to determine whether addition or substitution improves the predictive value of our proposed criteria.

With the addition of more minor criteria, the threshold for ICU admission was felt to be the presence of at least 3 minor criteria, based on the mortality association with the CURB criteria. Selecting 2 criteria appears to be too nonspecific, as is demonstrated by the initial ATS criteria [5]. Whether each of the criteria is of equal weight is also not clear. Therefore, prospective validation of this set of criteria is clearly needed.

## DIAGNOSTIC TESTING

9. In addition to a constellation of suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data, is required for the diagnosis of pneumonia. (Moderate recommendation; level III evidence.)

The diagnosis of CAP is based on the presence of select clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) and is supported by imaging of the lung, usually by chest radiography. Physical examination to detect rales or bronchial breath sounds is an important component of the evaluation but is less sensitive and specific than chest radiographs [96]. Both clinical features and physical exam findings may be lacking or altered in elderly patients. All patients should be screened by pulse oximetry, which may suggest both the presence of pneumonia in patients without obvious signs of pneumonia and unsuspected hypoxemia in patients with diagnosed pneumonia [42, 97, 98].

A chest radiograph is required for the routine evaluation of patients who are likely to have pneumonia, to establish the

diagnosis and to aid in differentiating CAP from other common causes of cough and fever, such as acute bronchitis. Chest radiographs are sometimes useful for suggesting the etiologic agent, prognosis, alternative diagnoses, and associated conditions. Rarely, the admission chest radiograph is clear, but the patient's toxic appearance suggests more than bronchitis. CT scans may be more sensitive, but the clinical significance of these findings when findings of radiography are negative is unclear [99]. For patients who are hospitalized for suspected pneumonia but who have negative chest radiography findings, it may be reasonable to treat their condition presumptively with antibiotics and repeat the imaging in 24–48 h.

Microbiological studies may support the diagnosis of pneumonia due to an infectious agent, but routine tests are frequently falsely negative and are often nonspecific. A history of recent travel or endemic exposure, if routinely sought, may identify specific potential etiologies that would otherwise be unexpected as a cause of CAP (see table 8) [100].

## Recommended Diagnostic Tests for Etiology

10. Patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues. (Strong recommendation; level II evidence.)

The need for diagnostic testing to determine the etiology of CAP can be justified from several perspectives. The primary reason for such testing is if results will change the antibiotic management for an individual patient. The spectrum of antibiotic therapy can be broadened, narrowed, or completely altered on the basis of diagnostic testing. The alteration in therapy that is potentially most beneficial to the individual is an escalation or switch of the usual empirical regimen because of unusual pathogens (e.g., endemic fungi or *Mycobacterium tuberculosis*) or antibiotic resistance issues. Broad empirical coverage, such as that recommended in these guidelines, would not provide the optimal treatment for certain infections, such as psittacosis or tularemia. Increased mortality [80] and increased risk of clinical failure [81, 101] are more common with inappropriate antibiotic therapy. Management of initial antibiotic failure is greatly facilitated by an etiologic diagnosis at admission. De-escalation or narrowing of antibiotic therapy on the basis of diagnostic testing is less likely to decrease an individual's risk of death but may decrease cost, drug adverse effects, and antibiotic resistance pressure.

Some etiologic diagnoses have important epidemiologic implications, such as documentation of severe acute respiratory syndrome (SARS), influenza, legionnaires disease, or agents of bioterrorism. Diagnostic testing for these infections may affect

**Table 5. Clinical indications for more extensive diagnostic testing.**

Indication	Blood culture	Sputum culture	<i>Legionella</i> UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X <sup>a</sup>
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X <sup>b</sup>
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X <sup>c</sup>
Positive <i>Legionella</i> UAT result		X <sup>d</sup>	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X <sup>e</sup>

**NOTE.** NA, not applicable; UAT, urinary antigen test.

<sup>a</sup> Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.

<sup>b</sup> Fungal and tuberculosis cultures.

<sup>c</sup> See table 8 for details.

<sup>d</sup> Special media for *Legionella*.

<sup>e</sup> Thoracentesis and pleural fluid cultures.

not only the individual but also many other people. Although pneumonia etiologies that should be reported to public health officials vary by state, in general, most states' health regulations require reporting of legionnaires disease, SARS, psittacosis, avian influenza (H5N1), and possible agents of bioterrorism (plague, tularemia, and anthrax). In addition, specific diagnostic testing and reporting are important for pneumonia cases of any etiology thought to be part of a cluster or caused by pathogens not endemic to the area.

There are also societal reasons for encouraging diagnostic testing. The antibiotic recommendations in the present guidelines are based on culture results and sensitivity patterns from patients with positive etiologic diagnoses [102]. Without the accumulated information available from these culture results, trends in antibiotic resistance are more difficult to track, and empirical antibiotic recommendations are less likely to be accurate.

The main downside of extensive diagnostic testing of all patients with CAP is cost, which is driven by the poor quality of most sputum microbiological samples and the low yield of positive culture results in many groups of patients with CAP. A clear need for improved diagnostic testing in CAP, most likely using molecular methodology rather than culture, has been recognized by the National Institutes of Health [103].

The cost-benefit ratio is even worse when antibiotic therapy is not streamlined when possible [104, 105] or when inappropriate escalation occurs [95]. In clinical practice, narrowing of antibiotic therapy is, unfortunately, unusual, but the committee strongly recommends this as best medical practice. The possibility of polymicrobial CAP and the potential benefit of combination therapy for bacteremic pneumococcal pneumonia

have complicated the decision to narrow antibiotic therapy. Delays in starting antibiotic therapy that result from the need to obtain specimens, complications of invasive diagnostic procedures, and unneeded antibiotic changes and additional testing for false-positive tests are also important considerations.

The general recommendation of the committee is to strongly encourage diagnostic testing whenever the result is likely to change individual antibiotic management. For other patients with CAP, the recommendations for diagnostic testing focus on patients in whom the diagnostic yield is thought to be greatest. These 2 priorities often overlap. Recommendations for patients in whom routine diagnostic testing is indicated for the above reasons are listed in table 5. Because of the emphasis on clinical relevance, a variety of diagnostic tests that may be accurate but the results of which are not available in a time window to allow clinical decisions are neither recommended nor discussed.

11. Routine diagnostic tests to identify an etiologic diagnosis are optional for outpatients with CAP. (Moderate recommendation; level III evidence.)

Retrospective studies of outpatient CAP management usually show that diagnostic tests to define an etiologic pathogen are infrequently performed, yet most patients do well with empirical antibiotic treatment [42, 106]. Exceptions to this general rule may apply to some pathogens important for epidemiologic reasons or management decisions. The availability of rapid point-of-care diagnostic tests, specific treatment and chemoprevention, and epidemiologic importance make influenza testing the most logical. Influenza is often suspected on the basis

of typical symptoms during the proper season in the presence of an epidemic. However, respiratory syncytial virus (RSV) can cause a similar syndrome and often occurs in the same clinical scenario [107]. Rapid diagnostic tests may be indicated when the diagnosis is uncertain and when distinguishing influenza A from influenza B is important for therapeutic decisions.

Other infections that are important to verify with diagnostic studies because of epidemiologic implications or because they require unique therapeutic intervention are SARS and avian (H5N1) influenza, disease caused by agents of bioterrorism, *Legionella* infection, community-acquired MRSA (CA-MRSA) infection, *M. tuberculosis* infection, or endemic fungal infection. Attempts to establish an etiologic diagnosis are also appropriate in selected cases associated with outbreaks, specific risk factors, or atypical presentations.

12. Pretreatment blood samples for culture and an expectorated sputum sample for stain and culture (in patients with a productive cough) should be obtained from hospitalized patients with the clinical indications listed in table 5 but are optional for patients without these conditions. (Moderate recommendation; level I evidence.)
13. Pretreatment Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures for collection, transport, and processing of samples can be met. (Moderate recommendation; level II evidence.)
14. Patients with severe CAP, as defined above, should at least have blood samples drawn for culture, urinary antigen tests for *Legionella pneumophila* and *S. pneumoniae* performed, and expectorated sputum samples collected for culture. For intubated patients, an endotracheal aspirate sample should be obtained. (Moderate recommendation; level II evidence.)

The only randomized controlled trial of diagnostic strategy in CAP has demonstrated no statistically significant differences in mortality rate or LOS between patients receiving pathogen-directed therapy and patients receiving empirical therapy [108]. However, pathogen-directed therapy was associated with lower mortality among the small number of patients admitted to the ICU. The study was performed in a country with a low incidence of antibiotic resistance, which may limit its applicability to areas with higher levels of resistance. Adverse effects were significantly more common in the empirical therapy group but may have been unique to the specific antibiotic choice (erythromycin).

The lack of benefit overall in this trial should not be interpreted as a lack of benefit for an individual patient. Therefore, performing diagnostic tests is never incorrect or a breach of the standard of care. However, information from cohort and

observational studies may be used to define patient groups in which the diagnostic yield is increased. Patient groups in which routine diagnostic testing is indicated and the recommended tests are listed in table 5.

**Blood cultures.** Pretreatment blood cultures yielded positive results for a probable pathogen in 5%–14% in large series of nonselected patients hospitalized with CAP [104, 105, 109–111]. The yield of blood cultures is, therefore, relatively low (although it is similar to yields in other serious infections), and, when management decisions are analyzed, the impact of positive blood cultures is minor [104, 105]. The most common blood culture isolate in all CAP studies is *S. pneumoniae*. Because this bacterial organism is always considered to be the most likely pathogen, positive blood culture results have not clearly led to better outcomes or improvements in antibiotic selection [105, 112]. False-positive blood culture results are associated with prolonged hospital stay, possibly related to changes in management based on preliminary results showing gram-positive cocci, which eventually prove to be coagulase-negative staphylococci [95, 109]. In addition, false-positive blood culture results have led to significantly more vancomycin use [95].

For these reasons, blood cultures are optional for all hospitalized patients with CAP but should be performed selectively (table 5). The yield for positive blood culture results is halved by prior antibiotic therapy [95]. Therefore, when performed, samples for blood culture should be obtained before antibiotic administration. However, when multiple risk factors for bacteremia are present, blood culture results after initiation of antibiotic therapy are still positive in up to 15% of cases [95] and are, therefore, still warranted in these cases, despite the lower yield.

The strongest indication for blood cultures is severe CAP. Patients with severe CAP are more likely to be infected with pathogens other than *S. pneumoniae*, including *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli [77–80, 95, 113, 114]. Many of the factors predictive of positive blood culture results [95] overlap with risk factors for severe CAP (table 4). Therefore, blood cultures are recommended for all patients with severe CAP because of the higher yield, the greater possibility of the presence of pathogens not covered by the usual empirical antibiotic therapy, and the increased potential to affect antibiotic management.

Blood cultures are also indicated when patients have a host defect in the ability to clear bacteremia—for example, as a result of asplenia or complement deficiencies. Patients with chronic liver disease also are more likely to have bacteremia with CAP [95]. Leukopenia is also associated with a high incidence of bacteremia [79, 95].

**Respiratory tract specimen Gram stain and culture.** The yield of sputum bacterial cultures is variable and strongly

influenced by the quality of the entire process, including specimen collection, transport, rapid processing, satisfactory use of cytologic criteria, absence of prior antibiotic therapy, and skill in interpretation. The yield of *S. pneumoniae*, for example, is only 40%–50% from sputum cultures from patients with bacteremic pneumococcal pneumonia in studies performed a few decades ago [115, 116]. A more recent study of 100 cases of bacteremic pneumococcal pneumonia found that sputum specimens were not submitted in 31% of cases and were judged as inadequate in another 16% of cases [117]. When patients receiving antibiotics for >24 h were excluded, Gram stain showed pneumococci in 63% of sputum specimens, and culture results were positive in 86%. For patients who had received no antibiotics, the Gram stain was read as being consistent with pneumococci in 80% of cases, and sputum culture results were positive in 93%.

Although there are favorable reports of the utility of Gram stain [118], a meta-analysis showed a low yield, considering the number of patients with adequate specimens and definitive results [119]. Recent data show that an adequate specimen with a predominant morphotype on Gram stain was found in only 14% of 1669 hospitalized patients with CAP [120]. Higher PSI scores did not predict higher yield. However, a positive Gram stain was highly predictive of a subsequent positive culture result.

The benefit of a sputum Gram stain is, therefore, 2-fold. First, it broadens initial empirical coverage for less common etiologies, such as infection with *S. aureus* or gram-negative organisms. This indication is probably the most important, because it will lead to less inappropriate antibiotic therapy. Second, it can validate the subsequent sputum culture results.

Forty percent or more of patients are unable to produce any sputum or to produce sputum in a timely manner [108, 120]. The yield of cultures is substantially higher with endotracheal aspirates, bronchoscopic sampling, or transthoracic needle aspirates [120–126], although specimens obtained after initiation of antibiotic therapy are unreliable and must be interpreted carefully [120, 127, 128]. Interpretation is improved with quantitative cultures of respiratory secretions from any source (sputum, tracheal aspirations, and bronchoscopic aspirations) or by interpretation based on semiquantitative culture results [122, 123, 129]. Because of the significant influence on diagnostic yield and cost effectiveness, careful attention to the details of specimen handling and processing are critical if sputum cultures are obtained.

Because the best specimens are collected and processed before antibiotics are given, the time to consider obtaining expectorated sputum specimens from patients with factors listed in table 5 is before initiation of antibiotic therapy. Once again, the best indication for more extensive respiratory tract cultures is severe CAP. Gram stain and culture of endotracheal aspirates

from intubated patients with CAP produce different results than expectorated sputum from non-ICU patients [76, 120]. Many of the pathogens in the broader microbiological spectrum of severe CAP are unaffected by a single dose of antibiotics, unlike *S. pneumoniae*. In addition, an endotracheal aspirate does not require patient cooperation, is clearly a lower respiratory tract sample, and is less likely to be contaminated by oropharyngeal colonizers. Nosocomial tracheal colonization is not an issue if the sample is obtained soon after intubation. Therefore, culture and Gram stain of endotracheal aspirates are recommended for patients intubated for severe CAP. In addition to routine cultures, a specific request for culture of respiratory secretions on buffered charcoal yeast extract agar to isolate *Legionella* species may be useful in this subset of patients with severe CAP in areas where *Legionella* is endemic, as well as in patients with a recent travel history [130].

The fact that a respiratory tract culture result is negative does not mean that it has no value. Failure to detect *S. aureus* or gram-negative bacilli in good-quality specimens is strong evidence against the presence of these pathogens. Growth inhibition by antibiotics is lower with these pathogens than with *S. pneumoniae*, but specimens obtained after initiation of antibiotic therapy are harder to interpret, with the possibility of colonization. Necrotizing or cavitary pneumonia is a risk for CA-MRSA infection, and sputum samples should be obtained in all cases. Negative Gram stain and culture results should be adequate to withhold or stop treatment for MRSA infection.

Severe COPD and alcoholism are major risk factors for infection with *P. aeruginosa* and other gram-negative pathogens [131]. Once again, Gram stain and culture of an adequate sputum specimen are usually adequate to exclude the need for empirical coverage of these pathogens.

A sputum culture in patients with suspected legionnaires disease is important, because the identification of *Legionella* species implies the possibility of an environmental source to which other susceptible individuals may be exposed. Localized community outbreaks of legionnaires disease might be recognized by clinicians or local health departments because  $\geq 2$  patients might be admitted to the same hospital. However, outbreaks of legionnaires disease associated with hotels or cruise ships [132–134] are rarely detected by individual clinicians, because travelers typically disperse from the source of infection before developing symptoms. Therefore, a travel history should be actively sought from patients with CAP, and *Legionella* testing should be performed for those who have traveled in the 2 weeks before the onset of symptoms. Urinary antigen tests may be adequate to diagnose and treat an individual, but efforts to obtain a sputum specimen for culture are still indicated to facilitate epidemiologic tracking. The availability of a culture isolate of *Legionella* dramatically improves the likelihood that an environmental source of *Legionella* can be identified and

remediated [135–137]. The yield of sputum culture is increased to 43%–57% when associated with a positive urinary antigen test result [138, 139].

Attempts to obtain a sample for sputum culture from a patient with a positive pneumococcal urinary antigen test result may be indicated for similar reasons. Patients with a productive cough and positive urinary antigen test results have positive sputum culture results in as many as 40%–80% of cases [140–143]. In these cases, not only can sensitivity testing confirm the appropriate choice for the individual patient, but important data regarding local community antibiotic resistance rates can also be acquired.

**Other cultures.** Patients with pleural effusions >5 cm in height on a lateral upright chest radiograph [111] should undergo thoracentesis to yield material for Gram stain and culture for aerobic and anaerobic bacteria. The yield with pleural fluid cultures is low, but the impact on management decisions is substantial, in terms of both antibiotic choice and the need for drainage.

Nonbronchoscopic bronchoalveolar lavage (BAL) in the ED has been studied in a small, randomized trial of intubated patients with CAP [144]. A high percentage (87%) of non-bronchoscopic BAL culture results were positive, even in some patients who had already received their first dose of antibiotics. Unfortunately, tracheal aspirates were obtained from only a third of patients in the control group, but they all were culture positive. Therefore, it is unclear that endotracheal aspirates are inferior to nonbronchoscopic BAL. The use of bronchoscopic BAL, protected specimen brushing, or transthoracic lung aspiration has not been prospectively studied for initial management of patients with CAP [123]. The best indications are for immunocompromised patients with CAP or for patients with CAP in whom therapy failed [101, 145].

**Antigen tests.** Urinary antigen tests are commercially available and have been cleared by the US Food and Drug Administration (FDA) for detection of *S. pneumoniae* and *L. pneumophila* serogroup 1 [138, 140, 146–149]. Urinary antigen testing appears to have a higher diagnostic yield in patients with more severe illness [139, 140].

For pneumococcal pneumonia, the principal advantages of antigen tests are rapidity (~15 min), simplicity, reasonable specificity in adults, and the ability to detect pneumococcal pneumonia after antibiotic therapy has been started. Studies in adults show a sensitivity of 50%–80% and a specificity of >90% [146, 149, 150]. This is an attractive test for detecting pneumococcal pneumonia when samples for culture cannot be obtained in a timely fashion or when antibiotic therapy has already been initiated. Serial specimens from patients with known bacteremia were still positive for pneumococcal urinary antigen in 83% of cases after 3 days of therapy [147]. Comparisons with Gram stain show that these 2 rapidly available tests often do

not overlap, with only 28% concordance (25 of 88) among patients when results of either test were positive [140]. Only ~50% of Binax pneumococcal urinary antigen–positive patients can be diagnosed by conventional methods [140, 150]. Disadvantages include cost (approximately \$30 per specimen), although this is offset by increased diagnosis-related group–based reimbursement for coding for pneumococcal pneumonia, and the lack of an organism for in vitro susceptibility tests. False-positive results have been seen in children with chronic respiratory diseases who are colonized with *S. pneumoniae* [151] and in patients with an episode of CAP within the previous 3 months [152], but they do not appear to be a significant problem in colonized patients with COPD [140, 152].

For *Legionella*, several urinary antigen assays are available, but all detect only *L. pneumophila* serogroup 1. Although this particular serogroup accounts for 80%–95% of community-acquired cases of legionnaires disease [138, 153] in many areas of North America, other species and serogroups predominate in specific locales [154, 155]. Prior studies of culture-proven legionnaires disease indicate a sensitivity of 70%–90% and a specificity of nearly 99% for detection of *L. pneumophila* serogroup 1. The urine is positive for antigen on day 1 of illness and continues to be positive for weeks [138, 150].

The major issue with urinary bacterial antigen detection is whether the tests allow narrowing of empirical antibiotic therapy to a single specific agent. The recommended empirical antibiotic regimens will cover both of these microorganisms. Results of a small observational study suggest that therapy with a macrolide alone is adequate for hospitalized patients with CAP who test positive for *L. pneumophila* urinary antigen [156]. Further research is needed in this area.

In contrast, rapid antigen detection tests for influenza, which can also provide an etiologic diagnosis within 15–30 min, can lead to consideration of antiviral therapy. Test performance varies according to the test used, sample type, duration of illness, and patient age. Most show a sensitivity of 50%–70% in adults and a specificity approaching 100% [157–159]. Advantages include the high specificity, the ability of some assays to distinguish between influenza A and B, the rapidity with which the results can be obtained, the possibly reduced use of antibacterial agents, and the utility of establishing this diagnosis for epidemiologic purposes, especially in hospitalized patients who may require infection control precautions. Disadvantages include cost (approximately \$30 per specimen), high rates of false-negative test results, false-positive assays with adenovirus infections, and the fact that the sensitivity is not superior to physician judgment among patients with typical symptoms during an influenza epidemic [157, 158, 160].

Direct fluorescent antibody tests are available for influenza and RSV and require ~2 h. For influenza virus, the sensitivity is better than with the point-of-care tests (85%–95%). They

will detect animal subtypes such as H5N1 and, thus, may be preferred for hospitalized patients [161, 162]. For RSV, direct fluorescent antibody tests are so insensitive (sensitivity, 20%–30%) in adults that they are rarely of value [163].

**Acute-phase serologic testing.** The standard for diagnosis of infection with most atypical pathogens, including *Chlamydomphila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* species other than *L. pneumophila*, relies on acute- and convalescent-phase serologic testing. Most studies use a microimmunofluorescence serologic test, but this test shows poor reproducibility [164]. Management of patients on the basis of a single acute-phase titer is unreliable [165], and initial antibiotic therapy will be completed before the earliest time point to check a convalescent-phase specimen.

**PCR.** A new PCR test (BD ProbeTec ET *Legionella pneumophila*; Becton Dickinson) that will detect all serotypes of *L. pneumophila* in sputum is now cleared by the FDA, but extensive published clinical experience is lacking. Most PCR reagents for other respiratory pathogens (except *Mycobacterium* species) are “home grown,” with requirements for use based on compliance with NCCLS criteria for analytical validity [166]. Despite the increasing use of these tests for atypical pathogens [167, 168], a 2001 review by the Centers for Disease Control and Prevention (CDC) of diagnostic assays for detection of *C. pneumoniae* indicated that, of the 18 PCR reagents, only 4 satisfied the criteria for a validated test [166]. The diagnostic criteria defined in this review are particularly important for use in prospective studies of CAP, because most prior reports used liberal criteria, which resulted in exaggerated rates. For SARS, several PCR assays have been developed, but these tests are inadequate because of high rates of false-negative assays in early stages of infection [169, 170].

## ANTIBIOTIC TREATMENT

A major goal of therapy is eradication of the infecting organism, with resultant resolution of clinical disease. As such, antimicrobials are a mainstay of treatment. Appropriate drug selection is dependent on the causative pathogen and its antibiotic susceptibility. Acute pneumonia may be caused by a wide variety of pathogens (table 6). However, until more accurate and rapid diagnostic methods are available, the initial treatment for most patients will remain empirical. Recommendations for therapy (table 7) apply to most cases; however, physicians should consider specific risk factors for each patient (table 8). A syndromic approach to therapy (under the assumption that an etiology correlates with the presenting clinical manifestations) is not specific enough to reliably predict the etiology of CAP [172–174]. Even if a microbial etiology is identified, debate continues with regard to pathogen-specific treatment, because recent studies suggest coinfection by atypical pathogens (such as *C. pneumoniae*, *Legionella* species, and viruses) and more tradi-

**Table 6. Most common etiologies of community-acquired pneumonia.**

Patient type	Etiology
Outpatient	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Haemophilus influenzae</i> <i>Chlamydomphila pneumoniae</i> Respiratory viruses <sup>a</sup>
Inpatient (non-ICU)	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>H. influenzae</i> <i>Legionella</i> species Aspiration Respiratory viruses <sup>a</sup>
Inpatient (ICU)	<i>S. pneumoniae</i> <i>Staphylococcus aureus</i> <i>Legionella</i> species Gram-negative bacilli <i>H. influenzae</i>

**NOTE.** Based on collective data from recent studies [171]. ICU, intensive care unit.

<sup>a</sup> Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

tional bacteria [120, 175]. However, the importance of treating multiple infecting organisms has not been firmly established.

The majority of antibiotics released in the past several decades have an FDA indication for CAP, making the choice of antibiotics potentially overwhelming. Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogen(s) and knowledge of local susceptibility patterns. Recommendations are generally for a class of antibiotics rather than a specific drug, unless outcome data clearly favor one drug. Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance. Other factors for consideration of specific antimicrobials include pharmacokinetics/pharmacodynamics, compliance, safety, and cost.

### Likely Pathogens in CAP

Although CAP may be caused by a myriad of pathogens, a limited number of agents are responsible for most cases. The emergence of newly recognized pathogens, such as the novel SARS-associated coronavirus [170], continually increases the challenge for appropriate management.

Table 6 lists the most common causes of CAP, in decreasing order of frequency of occurrence and stratified for severity of illness as judged by site of care (ambulatory vs. hospitalized). *S. pneumoniae* is the most frequently isolated pathogen. Other bacterial causes include nontypeable *Haemophilus influenzae*

**Table 7. Recommended empirical antibiotics for community-acquired pneumonia.**

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Outpatient treatment

1. Previously healthy and no use of antimicrobials within the previous 3 months
  - A macrolide (strong recommendation; level I evidence)
  - Doxycycline (weak recommendation; level III evidence)
2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
  - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
  - A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence)
3. In regions with a high rate (>25%) of infection with high-level (MIC  $\geq 16$   $\mu\text{g/mL}$ ) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation; level III evidence)

Inpatients, non-ICU treatment

- A respiratory fluoroquinolone (strong recommendation; level I evidence)
- A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment

- A  $\beta$ -lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) **or** a respiratory fluoroquinolone (level I evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Special concerns

- If *Pseudomonas* is a consideration
  - An antipseudomococcal, antipseudomonal  $\beta$ -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)
  - or**
  - The above  $\beta$ -lactam plus an aminoglycoside and azithromycin
  - or**
  - The above  $\beta$ -lactam plus an aminoglycoside and an antipseudomococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above  $\beta$ -lactam) (moderate recommendation; level III evidence)
- If CA-MRSA is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)

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**NOTE.** CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

and *Moraxella catarrhalis*, generally in patients who have underlying bronchopulmonary disease, and *S. aureus*, especially during an influenza outbreak. Risks for infection with Enterobacteriaceae species and *P. aeruginosa* as etiologies for CAP are chronic oral steroid administration or severe underlying bronchopulmonary disease, alcoholism, and frequent antibiotic therapy [79, 131], whereas recent hospitalization would define

cases as HCAP. Less common causes of pneumonia include, but are by no means limited to, *Streptococcus pyogenes*, *Neisseria meningitidis*, *Pasteurella multocida*, and *H. influenzae* type b.

The “atypical” organisms, so called because they are not detectable on Gram stain or cultivatable on standard bacteriologic media, include *M. pneumoniae*, *C. pneumoniae*, *Legionella* species, and respiratory viruses. With the exception of *Legionella* species, these microorganisms are common causes of pneumonia, especially among outpatients. However, these pathogens are not often identified in clinical practice because, with a few exceptions, such as *L. pneumophila* and influenza virus, no specific, rapid, or standardized tests for their detection exist. Although influenza remains the predominant viral cause of CAP in adults, other commonly recognized viruses include RSV [107], adenovirus, and parainfluenza virus, as well as less common viruses, including human metapneumovirus, herpes simplex virus, varicella-zoster virus, SARS-associated coronavirus, and measles virus. In a recent study of immunocompetent adult patients admitted to the hospital with CAP, 18% had evidence of a viral etiology, and, in 9%, a respiratory virus was the only pathogen identified [176]. Studies that include outpatients find viral pneumonia rates as high as 36% [167]. The frequency of other etiologic agents—for example, *M. tuberculosis*, *Chlamydia psittaci* (psittacosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), *Bordetella pertussis* (whooping cough), and endemic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Blastomyces hominis*)—is largely determined by the epidemiologic setting (table 8) but rarely exceeds 2%–3% total [113, 177]. The exception may be endemic fungi in the appropriate geographic distribution [100].

The need for specific anaerobic coverage for CAP is generally overestimated. Anaerobic bacteria cannot be detected by diagnostic techniques in current use. Anaerobic coverage is clearly indicated only in the classic aspiration pleuropulmonary syndrome in patients with a history of loss of consciousness as a result of alcohol/drug overdose or after seizures in patients with concomitant gingival disease or esophageal motility disorders. Antibiotic trials have not demonstrated a need to specifically treat these organisms in the majority of CAP cases. Small-volume aspiration at the time of intubation should be adequately handled by standard empirical severe CAP treatment [178] and by the high oxygen tension provided by mechanical ventilation.

### Antibiotic Resistance Issues

Resistance to commonly used antibiotics for CAP presents another major consideration in choosing empirical therapy. Resistance patterns clearly vary by geography. Local antibiotic prescribing patterns are a likely explanation [179–181]. However, clonal spread of resistant strains is well documented.

**Table 8. Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.**

Condition	Commonly encountered pathogen(s)
Alcoholism	<i>Streptococcus pneumoniae</i> , oral anaerobes, <i>Klebsiella pneumoniae</i> , <i>Acinetobacter</i> species, <i>Mycobacterium tuberculosis</i>
COPD and/or smoking	<i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Legionella</i> species, <i>S. pneumoniae</i> , <i>Moraxella cararrhalis</i> , <i>Chlamydophila pneumoniae</i>
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, <i>M. tuberculosis</i> , atypical mycobacteria
Exposure to bat or bird droppings	<i>Histoplasma capsulatum</i>
Exposure to birds	<i>Chlamydophila psittaci</i> (if poultry: avian influenza)
Exposure to rabbits	<i>Francisella tularensis</i>
Exposure to farm animals or parturient cats	<i>Coxiella burnetti</i> (Q fever)
HIV infection (early)	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. tuberculosis</i>
HIV infection (late)	The pathogens listed for early infection plus <i>Pneumocystis jirovecii</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Aspergillus</i> , atypical mycobacteria (especially <i>Mycobacterium kansasii</i> ), <i>P. aeruginosa</i> , <i>H. influenzae</i>
Hotel or cruise ship stay in previous 2 weeks	<i>Legionella</i> species
Travel to or residence in southwestern United States	<i>Coccidioides</i> species, <i>Hantavirus</i>
Travel to or residence in Southeast and East Asia	<i>Burkholderia pseudomallei</i> , avian influenza, SARS
Influenza active in community	Influenza, <i>S. pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>H. influenzae</i>
Cough >2 weeks with whoop or posttussive vomiting	<i>Bordetella pertussis</i>
Structural lung disease (e.g., bronchiectasis)	<i>Pseudomonas aeruginosa</i> , <i>Burkholderia cepacia</i> , <i>S. aureus</i>
Injection drug use	<i>S. aureus</i> , anaerobes, <i>M. tuberculosis</i> , <i>S. pneumoniae</i>
Endobronchial obstruction	Anaerobes, <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i>
In context of bioterrorism	<i>Bacillus anthracis</i> (anthrax), <i>Yersinia pestis</i> (plague), <i>Francisella tularensis</i> (tularemia)

**NOTE.** CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.

Therefore, antibiotic recommendations must be modified on the basis of local susceptibility patterns. The most reliable source is state/provincial or municipal health department regional data, if available. Local hospital antibiograms are generally the most accessible source of data but may suffer from small numbers of isolates.

**Drug-resistant *S. pneumoniae* (DRSP).** The emergence of drug-resistant pneumococcal isolates is well documented. The incidence of resistance appears to have stabilized somewhat in the past few years. Resistance to penicillin and cephalosporins may even be decreasing, whereas macrolide resistance continues to increase [179, 182]. However, the clinical relevance of DRSP for pneumonia is uncertain, and few well-controlled studies have examined the impact of in vitro resistance on clinical outcomes of CAP. Published studies are limited by small sample sizes, biases inherent in observational design, and the relative infrequency of isolates exhibiting high-level resistance [183–185]. Current levels of  $\beta$ -lactam resistance do not generally

result in CAP treatment failures when appropriate agents (i.e., amoxicillin, ceftriaxone, or cefotaxime) and doses are used, even in the presence of bacteremia [112, 186]. The available data suggest that the clinically relevant level of penicillin resistance is a MIC of at least 4 mg/L [3]. One report suggested that, if cefuroxime is used to treat pneumococcal bacteremia when the organism is resistant in vitro, the outcome is worse than with other therapies [112]. Other discordant therapies, including penicillin, did not have an impact on mortality. Data exist suggesting that resistance to macrolides [187–189] and older fluoroquinolones (ciprofloxacin and levofloxacin) [180, 190, 191] results in clinical failure. To date, no failures have been reported for the newer fluoroquinolones (moxifloxacin and gemifloxacin).

Risk factors for infection with  $\beta$ -lactam-resistant *S. pneumoniae* include age <2 years or >65 years,  $\beta$ -lactam therapy within the previous 3 months, alcoholism, medical comorbidities, immunosuppressive illness or therapy, and exposure to a

child in a day care center [112, 192–194]. Although the relative predictive value of these risk factors is unclear, recent treatment with antimicrobials is likely the most significant. Recent therapy or repeated courses of therapy with  $\beta$ -lactams, macrolides, or fluoroquinolones are risk factors for pneumococcal resistance to the same class of antibiotic [181, 193, 195, 196]. One study found that use of either a  $\beta$ -lactam or macrolide within the previous 6 months predicted an increased likelihood that, if pneumococcal bacteremia is present, the organism would be penicillin resistant [196]. Other studies have shown that repeated use of fluoroquinolones predicts an increased risk of infection with fluoroquinolone-resistant pneumococci [195, 197]. Whether this risk applies equally to all fluoroquinolones or is more of a concern for less active antipneumococcal agents (levofloxacin and ciprofloxacin) than for more active agents (moxifloxacin and gemifloxacin) is uncertain [190, 197, 198].

Recommendations for the use of highly active agents in patients at risk for infection with DRSP is, therefore, based only in part on efficacy considerations; it is also based on a desire to prevent more resistance from emerging by employing the most potent regimen possible. Although increasing the doses of certain agents (penicillins, cephalosporins, levofloxacin) may lead to adequate outcomes in the majority of cases, switching to more potent agents may lead to stabilization or even an overall decrease in resistance rates [179, 180].

**CA-MRSA.** Recently, an increasing incidence of pneumonia due to CA-MRSA has been observed [199, 200]. CA-MRSA appears in 2 patterns: the typical hospital-acquired strain [80] and, recently, strains that are epidemiologically, genotypically, and phenotypically distinct from hospital-acquired strains [201, 202]. Many of the former may represent HCAP, because these earlier studies did not differentiate this group from typical CAP. The latter are resistant to fewer antimicrobials than are hospital-acquired MRSA strains and often contain a novel type IV SCCmec gene. In addition, most contain the gene for Panton-Valentine leukocidin [200, 202], a toxin associated with clinical features of necrotizing pneumonia, shock, and respiratory failure, as well as formation of abscesses and empyemas. The large majority of cases published to date have been skin infections in children. In a large study of CA-MRSA in 3 communities, 2% of CA-MRSA infections were pneumonia [203]. However, pneumonia in both adults [204] and children has been reported, often associated with preceding influenza. This strain should also be suspected in patients who present with cavitary infiltrates without risk factors for anaerobic aspiration pneumonia (gingivitis and a risk for loss of consciousness, such as seizures or alcohol abuse, or esophageal motility disorders). Diagnosis is usually straightforward, with high yields from sputum and blood cultures in this characteristic clinical scenario. CA-MRSA CAP remains rare in most communities but is expected to be an emerging problem in CAP treatment.

## Empirical Antimicrobial Therapy

**Outpatient treatment.** The following regimens are recommended for outpatient treatment on the basis of the listed clinical risks.

15. Previously healthy and no risk factors for DRSP infection:
  - A. A macrolide (azithromycin, clarithromycin, or erythromycin) (strong recommendation; level I evidence)
  - B. Doxycycline (weak recommendation; level III evidence)
16. Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
  - A. A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
  - B. A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence) (High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-clavulanate [2 g 2 times daily] is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime [500 mg 2 times daily]; doxycycline [level II evidence] is an alternative to the macrolide.)
17. In regions with a high rate (>25%) of infection with high-level (MIC,  $\geq 16$   $\mu\text{g}/\text{mL}$ ) macrolide-resistant *S. pneumoniae*, consider the use of alternative agents listed above in recommendation 16 for any patient, including those without comorbidities. (Moderate recommendation; level III evidence.)

The most common pathogens identified from recent studies of mild (ambulatory) CAP were *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, and *H. influenzae* [177, 205]. *Mycoplasma* infection was most common among patients <50 years of age without significant comorbid conditions or abnormal vital signs, whereas *S. pneumoniae* was the most common pathogen among older patients and among those with significant underlying disease. *Hemophilus* infection was found in 5%—mostly in patients with comorbidities. The importance of therapy for *Mycoplasma* infection and *Chlamydothila* infection in mild CAP has been the subject of debate, because many infections are self-limiting [206, 207]. Nevertheless, studies from the 1960s of children indicate that treatment of mild *M. pneumoniae* CAP reduces the morbidity of pneumonia and shortens the duration of symptoms [208]. The evidence to support specific treatment of these microorganisms in adults is lacking.

Macrolides have long been commonly prescribed for treatment of outpatients with CAP in the United States, because of their activity against *S. pneumoniae* and the atypical pathogens.

This class includes the erythromycin-type agents (including dirithromycin), clarithromycin, and the azalide azithromycin. Although the least expensive, erythromycin is not often used now, because of gastrointestinal intolerance and lack of activity against *H. influenzae*. Because of *H. influenzae*, azithromycin is preferred for outpatients with comorbidities such as COPD.

Numerous randomized clinical trials have documented the efficacy of clarithromycin and azithromycin as monotherapy for outpatient CAP, although several studies have demonstrated that clinical failure can occur with a resistant isolate. When such patients were hospitalized and treated with a  $\beta$ -lactam and a macrolide, however, all survived and generally recovered without significant complications [188, 189]. Most of these patients had risk factors for which therapy with a macrolide alone is not recommended in the present guidelines. Thus, for patients with a significant risk of DRSP infection, monotherapy with a macrolide is not recommended. Doxycycline is included as a cost-effective alternative on the basis of in vitro data indicating effectiveness equivalent to that of erythromycin for pneumococcal isolates.

The use of fluoroquinolones to treat ambulatory patients with CAP without comorbid conditions, risk factors for DRSP, or recent antimicrobial use is discouraged because of concern that widespread use may lead to the development of fluoroquinolone resistance [185]. However, the fraction of total fluoroquinolone use specifically for CAP is extremely small and unlikely to lead to increased resistance by itself. More concerning is a recent study suggesting that many outpatients given a fluoroquinolone may not have even required an antibiotic, that the dose and duration of treatment were often incorrect, and that another agent often should have been used as first-line therapy. This usage pattern may promote the rapid development of resistance to fluoroquinolones [209].

Comorbidities or recent antimicrobial therapy increase the likelihood of infection with DRSP and enteric gram-negative bacteria. For such patients, recommended empirical therapeutic options include (1) a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg daily]) or (2) combination therapy with a  $\beta$ -lactam effective against *S. pneumoniae* plus a macrolide (doxycycline as an alternative). On the basis of present pharmacodynamic principles, high-dose amoxicillin (amoxicillin [1 g 3 times daily] or amoxicillin-clavulanate [2 g 2 times daily]) should target >93% of *S. pneumoniae* and is the preferred  $\beta$ -lactam. Ceftriaxone is an alternative to high-dose amoxicillin when parenteral therapy is feasible. Selected oral cephalosporins (cefepodoxime and cefuroxime) can be used as alternatives [210], but these are less active in vitro than high-dose amoxicillin or ceftriaxone. Agents in the same class as the patient had been receiving previously should not be used to treat patients with recent antibiotic exposure.

Telithromycin is the first of the ketolide antibiotics, derived

from the macrolide family, and is active against *S. pneumoniae* that is resistant to other antimicrobials commonly used for CAP (including penicillin, macrolides, and fluoroquinolones). Several CAP trials suggest that telithromycin is equivalent to comparators (including amoxicillin, clarithromycin, and trovafloxacin) [211–214]. There have also been recent postmarketing reports of life-threatening hepatotoxicity [215]. At present, the committee is awaiting further evaluation of the safety of this drug by the FDA before making its final recommendation.

**Inpatient, non-ICU treatment.** The following regimens are recommended for hospital ward treatment.

18. A respiratory fluoroquinolone (strong recommendation; level I evidence)
19. A  $\beta$ -lactam **plus** a macrolide (strong recommendation; level I evidence) (Preferred  $\beta$ -lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline [level III evidence] as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients.)

The recommendations of combination treatment with a  $\beta$ -lactam plus a macrolide or monotherapy with a fluoroquinolone were based on retrospective studies demonstrating a significant reduction in mortality compared with that associated with administration of a cephalosporin alone [216–219]. Multiple prospective randomized trials have demonstrated that either regimen results in high cure rates. The major discriminating factor between the 2 regimens is the patient's prior antibiotic exposure (within the past 3 months).

Preferred  $\beta$ -lactams are those effective against *S. pneumoniae* and other common, nonatypical pathogens without being overly broad spectrum. In January 2002, the Clinical Laboratory Standards Institute (formerly the NCCLS) increased the MIC breakpoints for cefotaxime and ceftriaxone for nonmeningeal *S. pneumoniae* infections. These new breakpoints acknowledge that nonmeningeal infections caused by strains formerly considered to be intermediately susceptible, or even resistant, can be treated successfully with usual doses of these  $\beta$ -lactams [112, 186, 220].

Two randomized, double-blind studies showed ertapenem to be equivalent to ceftriaxone [221, 222]. It also has excellent activity against anaerobic organisms, DRSP, and most Enterobacteriaceae species (including extended-spectrum  $\beta$ -lactamase producers, but not *P. aeruginosa*). Ertapenem may be useful in treating patients with risks for infection with these pathogens and for patients who have recently received antibiotic therapy. However, clinical experience with this agent is limited. Other "antipneumococcal, antipseudomonal"  $\beta$ -lactam agents are appropriate when resistant pathogens, such as *Pseudomonas*, are likely to be present. Doxycycline can be used as an alter-

native to a macrolide on the basis of scant data for treatment of *Legionella* infections [171, 223, 224].

Two randomized, double-blind studies of adults hospitalized for CAP have demonstrated that parenteral azithromycin alone was as effective, with improved tolerability, as intravenous cefuroxime, with or without intravenous erythromycin [225, 226]. In another study, mortality and readmission rates were similar, but the mean LOS was shorter among patients receiving azithromycin alone than among those receiving other guideline-recommended therapy [227]. None of the 10 patients with erythromycin-resistant *S. pneumoniae* infections died or was transferred to the ICU, including 6 who received azithromycin alone. Another study showed that those receiving a macrolide alone had the lowest 30-day mortality but were the least ill [219]. Such patients were younger and were more likely to be in lower-risk groups.

These studies suggest that therapy with azithromycin alone can be considered for carefully selected patients with CAP with nonsevere disease (patients admitted primarily for reasons other than CAP) and no risk factors for infection with DRSP or gram-negative pathogens. However, the emergence of high rates of macrolide resistance in many areas of the country suggests that this therapy cannot be routinely recommended. Initial therapy should be given intravenously for most admitted patients, but some without risk factors for severe pneumonia could receive oral therapy, especially with highly bioavailable agents such as fluoroquinolones. When an intravenous  $\beta$ -lactam is combined with coverage for atypical pathogens, oral therapy with a macrolide or doxycycline is appropriate for selected patients without severe pneumonia risk factors [228].

**Inpatient, ICU treatment.** The following regimen is the minimal recommended treatment for patients admitted to the ICU.

20. A  $\beta$ -lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) or a fluoroquinolone (level I evidence) (strong recommendation) (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)

A single randomized controlled trial of treatment for severe CAP is available. Patients with shock were excluded; however, among the patients with mechanical ventilation, treatment with a fluoroquinolone alone resulted in a trend toward inferior outcome [229]. Because septic shock and mechanical ventilation are the clearest reasons for ICU admission, the majority of ICU patients would still require combination therapy. ICU patients are routinely excluded from other trials; therefore, recommendations are extrapolated from nonsevere cases, in conjunction with case series and retrospective analyses of cohorts with severe CAP.

For all patients admitted to the ICU, coverage for *S. pneu-*

*moniae* and *Legionella* species should be ensured [78, 230] by using a potent antipneumococcal  $\beta$ -lactam and either a macrolide or a fluoroquinolone. Therapy with a respiratory fluoroquinolone alone is not established for severe CAP [229], and, if the patient has concomitant pneumococcal meningitis, the efficacy of fluoroquinolone monotherapy is uncertain. In addition, 2 prospective observational studies [231, 232] and 3 retrospective analyses [233–235] have found that combination therapy for bacteremic pneumococcal pneumonia is associated with lower mortality than monotherapy. The mechanism of this benefit is unclear but was principally found in the patients with the most severe illness and has not been demonstrated in nonbacteremic pneumococcal CAP studies. Therefore, combination empirical therapy is recommended for at least 48 h or until results of diagnostic tests are known.

In critically ill patients with CAP, a large number of microorganisms other than *S. pneumoniae* and *Legionella* species must be considered. A review of 9 studies that included 890 patients with CAP who were admitted to the ICU demonstrates that the most common pathogens in the ICU population were (in descending order of frequency) *S. pneumoniae*, *Legionella* species, *H. influenzae*, Enterobacteriaceae species, *S. aureus*, and *Pseudomonas* species [171]. The atypical pathogens responsible for severe CAP may vary over time but can account collectively for  $\geq 20\%$  of severe pneumonia episodes. The dominant atypical pathogen in severe CAP is *Legionella* [230], but some diagnostic bias probably accounts for this finding [78].

The recommended standard empirical regimen should routinely cover the 3 most common pathogens that cause severe CAP, all of the atypical pathogens, and most of the relevant Enterobacteriaceae species. Treatment of MRSA or *P. aeruginosa* infection is the main reason to modify the standard empirical regimen. The following are additions or modifications to the basic empirical regimen recommended above if these pathogens are suspected.

21. For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal  $\beta$ -lactam (piperacillin-tazobactam, ceftepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose)
  - or**
  - the above  $\beta$ -lactam plus an aminoglycoside and azithromycin
  - or**
  - the above  $\beta$ -lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone. (For penicillin-allergic patients, substitute aztreonam for the above  $\beta$ -lactam.)(Moderate recommendation; level III evidence.)

Pseudomonal CAP requires combination treatment to prevent inappropriate initial therapy, just as *Pseudomonas* noso-

comial pneumonia does [131]. Once susceptibilities are known, treatment can be adjusted accordingly. Alternative regimens are provided for patients who may have recently received an oral fluoroquinolone, in whom the aminoglycoside-containing regimen would be preferred. A consistent Gram stain of tracheal aspirate, sputum, or blood is the best indication for *Pseudomonas* coverage. Other, easier-to-treat gram-negative microorganisms may ultimately be proven to be the causative pathogen, but empirical coverage of *Pseudomonas* species until culture results are known is least likely to be associated with inappropriate therapy. Other clinical risk factors for infection with *Pseudomonas* species include structural lung diseases, such as bronchiectasis, or repeated exacerbations of severe COPD leading to frequent steroid and/or antibiotic use, as well as prior antibiotic therapy [131]. These patients do not necessarily require ICU admission for CAP [236], so *Pseudomonas* infection remains a concern for them even if they are only hospitalized on a general ward. The major risk factor for infection with other serious gram-negative pathogens, such as *Klebsiella pneumoniae* or *Acinetobacter* species, is chronic alcoholism.

22. For CA-MRSA infection, add vancomycin or linezolid. (Moderate recommendation; level III evidence.)

The best indicator of *S. aureus* infection is the presence of gram-positive cocci in clusters in a tracheal aspirate or in an adequate sputum sample. The same findings on preliminary results of blood cultures are not as reliable, because of the significant risk of contamination [95]. Clinical risk factors for *S. aureus* CAP include end-stage renal disease, injection drug abuse, prior influenza, and prior antibiotic therapy (especially with fluoroquinolones [237]).

For methicillin-sensitive *S. aureus*, the empirical combination therapy recommended above, which includes a  $\beta$ -lactam and sometimes a respiratory fluoroquinolone, should be adequate until susceptibility results are available and specific therapy with a penicillinase-resistant semisynthetic penicillin or first-generation cephalosporin can be initiated. Both also offer additional coverage for DRSP. Neither linezolid [241] nor vancomycin [238] is an optimal drug for methicillin-sensitive *S. aureus*.

Although methicillin-resistant strains of *S. aureus* are still the minority, the excess mortality associated with inappropriate antibiotic therapy [80] would suggest that empirical coverage should be considered when CA-MRSA is a concern. The most effective therapy has yet to be defined. The majority of CA-MRSA strains are more susceptible in vitro to non- $\beta$ -lactam antimicrobials, including trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones, than are hospital-acquired strains. Previous experience with TMP-SMX in other types of severe infections (endocarditis and septic thrombophlebitis) suggests that

TMP-SMX is inferior to vancomycin [239]. Further experience and study of the adequacy of TMP-SMX for CA-MRSA CAP is clearly needed. Vancomycin has never been specifically studied for CAP, and linezolid has been found to be better than ceftriaxone for bacteremic *S. pneumoniae* in a nonblinded study [240] and superior to vancomycin in retrospective analysis of studies involving nosocomial MRSA pneumonia [241]. Newer agents for MRSA have recently become available, and others are anticipated. Of the presently available agents, daptomycin should not be used for CAP, and no data on pneumonia are available for tigecycline.

A concern with CA-MRSA is necrotizing pneumonia associated with production of Panton-Valentine leukocidin and other toxins. Vancomycin clearly does not decrease toxin production, and the effect of TMP-SMX and fluoroquinolones on toxin production is unclear. Addition of clindamycin or use of linezolid, both of which have been shown to affect toxin production in a laboratory setting [242], may warrant their consideration for treatment of these necrotizing pneumonias [204]. Unfortunately, the emergence of resistance during therapy with clindamycin has been reported (especially in erythromycin-resistant strains), and vancomycin would still be needed for bacterial killing.

### Pathogens Suspected on the Basis of Epidemiologic Considerations

Clinicians should be aware of epidemiologic conditions and/or risk factors that may suggest that alternative or specific additional antibiotics should be considered. These conditions and specific pathogens, with preferred treatment, are listed in tables 8 and 9.

### Pathogen-Directed Therapy

23. Once the etiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen. (Moderate recommendation; level III evidence.)

Treatment options may be simplified (table 9) if the etiologic agent is established or strongly suspected. Diagnostic procedures that identify a specific etiology within 24–72 h can still be useful for guiding continued therapy. This information is often available at the time of consideration for a switch from parenteral to oral therapy and may be used to direct specific oral antimicrobial choices. If, for example, an appropriate culture reveals penicillin-susceptible *S. pneumoniae*, a narrow-spectrum agent (such as penicillin or amoxicillin) may be used. This will, hopefully, reduce the selective pressure for resistance.

The major issue with pathogen-specific therapy is management of bacteremic *S. pneumoniae* CAP. The implications of the observational finding that dual therapy was associated with

**Table 9. Recommended antimicrobial therapy for specific pathogens.**

Organism	Preferred antimicrobial(s)	Alternative antimicrobial(s)
<i>Streptococcus pneumoniae</i>		
Penicillin nonresistant; MIC <2 µg/mL	Penicillin G, amoxicillin	Macrolide, cephalosporins (oral [cefepodoxime, cefprozil, cefuroxime, cefdinir, cefditoren] or parenteral [cefuroxime, ceftriaxone, cefotaxime]), clindamycin, doxycycline, respiratory fluoroquinolone <sup>a</sup>
Penicillin resistant; MIC ≥2 µg/mL	Agents chosen on the basis of susceptibility, including cefotaxime, ceftriaxone, fluoroquinolone	Vancomycin, linezolid, high-dose amoxicillin (3 g/day with penicillin MIC ≤4 µg/mL)
<i>Haemophilus influenzae</i>		
Non-β-lactamase producing	Amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin <sup>b</sup>
β-Lactamase producing	Second- or third-generation cephalosporin, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin <sup>b</sup>
<i>Mycoplasma pneumoniae/Chlamydia pneumoniae</i>	Macrolide, a tetracycline	Fluoroquinolone
<i>Legionella</i> species	Fluoroquinolone, azithromycin	Doxycycline
<i>Chlamydia psittaci</i>	A tetracycline	Macrolide
<i>Coxiella burnetii</i>	A tetracycline	Macrolide
<i>Francisella tularensis</i>	Doxycycline	Gentamicin, streptomycin
<i>Yersinia pestis</i>	Streptomycin, gentamicin	Doxycycline, fluoroquinolone
<i>Bacillus anthracis</i> (inhalation)	Ciprofloxacin, levofloxacin, doxycycline (usually with second agent)	Other fluoroquinolones; β-lactam, if susceptible; rifampin; clindamycin; chloramphenicol
Enterobacteriaceae	Third-generation cephalosporin, carbapenem <sup>c</sup> (drug of choice if extended-spectrum β-lactamase producer)	β-Lactam/β-lactamase inhibitor, <sup>d</sup> fluoroquinolone
<i>Pseudomonas aeruginosa</i>	Antipseudomonal β-lactam <sup>e</sup> <b>plus</b> (ciprofloxacin or levofloxacin <sup>f</sup> or aminoglycoside)	Aminoglycoside <b>plus</b> (ciprofloxacin or levofloxacin <sup>f</sup> )
<i>Burkholderia pseudomallei</i>	Carbapenem, ceftazidime	Fluoroquinolone, TMP-SMX
<i>Acinetobacter</i> species	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin
<i>Staphylococcus aureus</i>		
Methicillin susceptible	Antistaphylococcal penicillin <sup>g</sup>	Cefazolin, clindamycin
Methicillin resistant	Vancomycin or linezolid	TMP-SMX
<i>Bordetella pertussis</i>	Macrolide	TMP-SMX
Anaerobe (aspiration)	β-Lactam/β-lactamase inhibitor, <sup>d</sup> clindamycin	Carbapenem
Influenza virus	Oseltamivir or zanamivir	
<i>Mycobacterium tuberculosis</i>	Isoniazid plus rifampin plus ethambutol plus pyrazinamide	Refer to [243] for specific recommendations
<i>Coccidioides</i> species	For uncomplicated infection in a normal host, no therapy generally recommended; for therapy, itraconazole, fluconazole	Amphotericin B
Histoplasmosis	Itraconazole	Amphotericin B
Blastomycosis	Itraconazole	Amphotericin B

**NOTE.** Choices should be modified on the basis of susceptibility test results and advice from local specialists. Refer to local references for appropriate doses. ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup> Levofloxacin, moxifloxacin, gemifloxacin (not a first-line choice for penicillin susceptible strains); ciprofloxacin is appropriate for *Legionella* and most gram-negative bacilli (including *H. influenzae*).

<sup>b</sup> Azithromycin is more active in vitro than clarithromycin for *H. influenzae*.

<sup>c</sup> Imipenem-cilastatin, meropenem, ertapenem.

<sup>d</sup> Piperacillin-tazobactam for gram-negative bacilli, ticarcillin-clavulanate, ampicillin-sulbactam or amoxicillin-clavulanate.

<sup>e</sup> Ticarcillin, piperacillin, ceftazidime, cefepime, aztreonam, imipenem, meropenem.

<sup>f</sup> 750 mg daily.

<sup>g</sup> Nafcillin, oxacillin flucloxacillin.

reduced mortality in bacteremic pneumococcal pneumonia [231–235] are uncertain. One explanation for the reduced mortality may be the presence of undiagnosed coinfection with an atypical pathogen; although reported to occur in 18%–38% of CAP cases in some studies [73, 175], much lower rates of undiagnosed coinfection are found in general [171] and specifically in severe cases [78]. An alternative explanation is the immunomodulatory effects of macrolides [244, 245]. It is important to note that these studies evaluated the effects of initial empirical therapy before the results of blood cultures were known and did not examine effects of pathogen-specific therapy after the results of blood cultures were available. The benefit of combination therapy was also most pronounced in the more severely ill patients [233, 234]. Therefore, discontinuation of combination therapy after results of cultures are known is most likely safe in non-ICU patients.

24. Early treatment (within 48 h of onset of symptoms) with oseltamivir or zanamivir is recommended for influenza A. (Strong recommendation; level I evidence.)
25. Use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 h (level I evidence), but these drugs may be used to reduce viral shedding in hospitalized patients or for influenza pneumonia. (Moderate recommendation; level III evidence.)

Studies that demonstrate that treatment of influenza is effective only if instituted within 48 h of the onset of symptoms have been performed only in uncomplicated cases [246–249]. The impact of such treatment on patients who are hospitalized with influenza pneumonia or a bacterial pneumonia complicating influenza is unclear. In hospitalized adults with influenza, a minority of whom had radiographically documented pneumonia, no obvious benefit was found in one retrospective study of amantadine treatment [250]. Treatment of antigen- or culture-positive patients with influenza with antivirals in addition to antibiotics is warranted, even if the radiographic infiltrate is caused by a subsequent bacterial superinfection. Because of the longer period of persistent positivity after infection, the appropriate treatment for patients diagnosed with only 1 of the rapid diagnostic tests is unclear. Because such patients often have recoverable virus (median duration of 4 days) after hospitalization, antiviral treatment seems reasonable from an infection-control standpoint alone.

Because of its broad influenza spectrum, low risk of resistance emergence, and lack of bronchospasm risk, oseltamivir is an appropriate choice for hospitalized patients. The neuraminidase inhibitors are effective against both influenza A and B viruses, whereas the M2 inhibitors, amantadine, and rimantadine are active only against influenza A [251]. In addition, viruses re-

cently circulating in the United States and Canada are often resistant to the M2 inhibitors on the basis of antiviral testing [252, 253]. Therefore, neither amantadine nor rimantadine should be used for treatment or chemoprophylaxis of influenza A in the United States until susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses [249].

Early treatment of influenza in ambulatory adults with inhaled zanamivir or oral oseltamivir appears to reduce the likelihood of lower respiratory tract complications [254–256]. The use of influenza antiviral medications appears to reduce the likelihood of respiratory tract complications, as reflected by reduced usage rates of antibacterial agents in ambulatory patients with influenza. Although clearly important in outpatient pneumonia, this experience may also apply to patients hospitalized primarily for influenza.

Parenteral acyclovir is indicated for treatment of varicella-zoster virus infection [257] or herpes simplex virus pneumonia. No antiviral treatment of proven value is available for other viral pneumonias—that is, parainfluenza virus, RSV, adenovirus, metapneumovirus, the SARS agent, or hantavirus. For all patients with viral pneumonias, a high clinical suspicion of bacterial superinfection should be maintained.

#### ***Pandemic influenza.***

26. Patients with an illness compatible with influenza and with known exposure to poultry in areas with previous H5N1 infection should be tested for H5N1 infection. (Moderate recommendation; level III evidence.)
27. In patients with suspected H5N1 infection, droplet precautions and careful routine infection control measures should be used until an H5N1 infection is ruled out. (Moderate recommendation; level III evidence.)
28. Patients with suspected H5N1 infection should be treated with oseltamivir (level II evidence) and antibacterial agents targeting *S. pneumoniae* and *S. aureus*, the most common causes of secondary bacterial pneumonia in patients with influenza (level III evidence). (Moderate recommendation.)

Recent human infections caused by avian influenza A (H5N1) in Vietnam, Thailand, Cambodia, China, Indonesia, Egypt, and Turkey raise the possibility of a pandemic in the near future. The severity of H5N1 infection in humans distinguishes it from that caused by routine seasonal influenza. Respiratory failure requiring hospitalization and intensive care has been seen in the majority of the >140 recognized cases, and mortality is ~50% [258, 259]. If a pandemic occurs, deaths will result from primary influenza pneumonia with or without secondary bacterial pneumonia. This section highlights issues for consideration, recognizing that treatment recommendations

will likely change as the pandemic progresses. More specific guidance can be found on the IDSA, ATS, CDC, and WHO Web sites as the key features of the pandemic become clearer. Additional guidance is available at <http://www.pandemicflu.gov>.

The WHO has delineated 6 phases of an influenza pandemic, defined by increasing levels of risk and public health response [260]. During the current pandemic alert phase (phase 3: cases of novel influenza infection without sustained person-to-person transmission), testing should be focused on confirming all suspected cases in areas where H5N1 infection has been documented in poultry and on detecting the arrival of the pandemic strain in unaffected countries. Early clinical features of H5N1 infection include persistent fever, cough, and respiratory difficulty progressing over 3–5 days, as well as lymphopenia on admission to the hospital [258, 259, 261]. Exposure to sick and dying poultry in an area with known or suspected H5N1 activity has been reported by most patients, although the recognition of poultry outbreaks has sometimes followed the recognition of human cases [261].

Rapid bedside tests to detect influenza A have been used as screening tools for avian influenza in some settings. Throat swabs tested by RT-PCR have been the most sensitive for confirming H5N1 infection to date, but nasopharyngeal swabs, washes, and aspirates; BAL fluid; lung and other tissues; and stool have yielded positive results by RT-PCR and viral culture with varying sensitivity. Convalescent-phase serum can be tested by microneutralization for antibodies to H5 antigen in a small number of international reference laboratories. Specimens from suspected cases of H5N1 infection should be sent to public health laboratories with appropriate biocontainment facilities; the case should be discussed with health department officials to arrange the transfer of specimens and to initiate an epidemiologic evaluation. During later phases of an ongoing pandemic, testing may be necessary for many more patients, so that appropriate treatment and infection control decisions can be made, and to assist in defining the extent of the pandemic. Recommendations for such testing will evolve on the basis of the features of the pandemic, and guidance should be sought from the CDC and WHO Web sites (<http://www.cdc.gov> and <http://www.who.int>).

Patients with confirmed or suspected H5N1 influenza should be treated with oseltamivir. Most H5N1 isolates since 2004 have been susceptible to the neuraminidase inhibitors oseltamivir and zanamivir and resistant to the adamantanes (amantidine and rimantidine) [262, 263]. The current recommendation is for a 5-day course of treatment at the standard dosage of 75 mg 2 times daily. In addition, droplet precautions should be used for patients with suspected H5N1 influenza, and they should be placed in respiratory isolation until that etiology is ruled out. Health care personnel should wear N-95 (or higher)

respirators during medical procedures that have a high likelihood of generating infectious respiratory aerosols.

Bacterial superinfections, particularly pneumonia, are important complications of influenza pneumonia. The bacterial etiologies of CAP after influenza infection have included *S. pneumoniae*, *S. aureus*, *H. influenzae*, and group A streptococci. *Legionella*, *Chlamydia*, and *Mycoplasma* species are not important causes of secondary bacterial pneumonia after influenza. Appropriate agents would therefore include cefotaxime, ceftriaxone, and respiratory fluoroquinolones. Treatment with vancomycin, linezolid, or other agents directed against CA-MRSA should be limited to patients with confirmed infection or a compatible clinical presentation (shock and necrotizing pneumonia). Because shortages of antibacterials and antivirals are anticipated during a pandemic, the appropriate use of diagnostic tests will be even more important to help target antibacterial therapy whenever possible, especially for patients admitted to the hospital.

#### Time to First Antibiotic Dose

29. For patients admitted through the ED, the first antibiotic dose should be administered while still in the ED. (Moderate recommendation; level III evidence.)

Time to first antibiotic dose for CAP has recently received significant attention from a quality-of-care perspective. This emphasis is based on 2 retrospective studies of Medicare beneficiaries that demonstrated statistically significantly lower mortality among patients who received early antibiotic therapy [109, 264]. The initial study suggested a breakpoint of 8 h [264], whereas the subsequent analysis found that 4 h was associated with lower mortality [109]. Studies that document the time to first antibiotic dose do not consistently demonstrate this difference, although none had as large a patient population. Most importantly, prospective trials of care by protocol have not demonstrated a survival benefit to increasing the percentage of patients with CAP who receive antibiotics within the first 4–8 h [22, 65]. Early antibiotic administration does not appear to shorten the time to clinical stability, either [265], although time of first dose does appear to correlate with LOS [266, 267]. A problem of internal consistency is also present, because, in both studies [109, 264], patients who received antibiotics in the first 2 h after presentation actually did worse than those who received antibiotics 2–4 h after presentation. For these and other reasons, the committee did not feel that a specific time window for delivery of the first antibiotic dose should be recommended. However, the committee does feel that therapy should be administered as soon as possible after the diagnosis is considered likely.

Conversely, a delay in antibiotic therapy has adverse conse-

quences in many infections. For critically ill, hemodynamically unstable patients, early antibiotic therapy should be encouraged, although no prospective data support this recommendation. Delay in beginning antibiotic treatment during the transition from the ED is not uncommon. Especially with the frequent use of once-daily antibiotics for CAP, timing and communication issues may result in patients not receiving antibiotics for >8 h after hospital admission. The committee felt that the best and most practical resolution to this issue was that the initial dose be given in the ED [22].

Data from the Medicare database indicated that antibiotic treatment before hospital admission was also associated with lower mortality [109]. Given that there are even more concerns regarding timing of the first dose of antibiotic when the patient is directly admitted to a busy inpatient unit, provision of the first dose in the physician's office may be best if the recommended oral or intramuscular antibiotics are available in the office.

### Switch from Intravenous to Oral Therapy

30. Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract. (Strong recommendation; level II evidence.)
31. Patients should be discharged as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is not necessary. (Moderate recommendation; level II evidence.)

With the use of a potent, highly bioavailable antibiotic, the ability to eat and drink is the major consideration for switching from intravenous to oral antibiotic therapy for non-ICU patients. Initially, Ramirez et al. [268] defined a set of criteria for an early switch from intravenous to oral therapy (table 10). In general, as many as two-thirds of all patients have clinical improvement and meet criteria for a therapy switch in the first 3 days, and most non-ICU patients meet these criteria by day 7.

Subsequent studies have suggested that even more liberal criteria are adequate for the switch to oral therapy. An alternative approach is to change from intravenous to oral therapy at a predetermined time, regardless of the clinical response [269]. One study population with nonsevere illness was randomized to receive either oral therapy alone or intravenous therapy, with the switch occurring after 72 h without fever. The study population with severe illness was randomized to receive either intravenous therapy with a switch to oral therapy after 2 days or a full 10-day course of intravenous antibiotics. Time

**Table 10. Criteria for clinical stability.**

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Temperature $\leq 37.8^{\circ}\text{C}$
Heart rate $\leq 100$ beats/min
Respiratory rate $\leq 24$ breaths/min
Systolic blood pressure $\geq 90$ mm Hg
Arterial oxygen saturation $\geq 90\%$ or $\text{pO}_2 \geq 60$ mm Hg on room air
Ability to maintain oral intake <sup>a</sup>
Normal mental status <sup>a</sup>

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**NOTE.** Criteria are from [268, 274, 294].  $\text{pO}_2$ , oxygen partial pressure.

<sup>a</sup> Important for discharge or oral switch decision but not necessarily for determination of nonresponse.

to resolution of symptoms for the patients with nonsevere illness was similar with either regimen. Among patients with more severe illness, the rapid switch to oral therapy had the same rate of treatment failure and the same time to resolution of symptoms as prolonged intravenous therapy. The rapid-switch group required fewer inpatient days (6 vs. 11), although this was likely partially a result of the protocol, but the patients also had fewer adverse events.

The need to keep patients in the hospital once clinical stability is achieved has been questioned, even though physicians commonly choose to observe patients receiving oral therapy for  $\geq 1$  day. Even in the presence of pneumococcal bacteremia, a switch to oral therapy can be safely done once clinical stability is achieved and prolonged intravenous therapy is not needed [270]. Such patients generally take longer (approximately half a day) to become clinically stable than do nonbacteremic patients. The benefits of in-hospital observation after a switch to oral therapy are limited and add to the cost of care [32].

Discharge should be considered when the patient is a candidate for oral therapy and when there is no need to treat any comorbid illness, no need for further diagnostic testing, and no unmet social needs [32, 271, 272]. Although it is clear that clinically stable patients can be safely switched to oral therapy and discharged, the need to wait for all of the features of clinical stability to be present before a patient is discharged is uncertain. For example, not all investigators have found it necessary to have the white blood cell count improve. Using the definition for clinical stability in table 10, Halm et al. [273] found that 19.1% of 680 patients were discharged from the hospital with  $\geq 1$  instability. Death or readmission occurred in 10.5% of patients with no instability on discharge, in 13.7% of patients with 1 instability, and in 46.2% with  $\geq 2$  instabilities. In general, patients in higher PSI classes take longer to reach clinical stability than do patients in lower risk classes [274]. This finding may reflect the fact that elderly patients with multiple comorbidities often recover more slowly. Arrangements for appropriate follow-up care, including rehabilitation, should therefore be initiated early for these patients.

In general, when switching to oral antibiotics, either the same

agent as the intravenous antibiotic or the same drug class should be used. Switching to a different class of agents simply because of its high bioavailability (such as a fluoroquinolone) is probably not necessary for a responding patient. For patients who received intravenous  $\beta$ -lactam–macrolide combination therapy, a switch to a macrolide alone appears to be safe for those who do not have DRSP or gram-negative enteric pathogens isolated [275].

### Duration of Antibiotic Therapy

32. Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy (level II evidence). (Moderate recommendation.)
33. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis. (Weak recommendation; level III evidence.)

Most patients with CAP have been treated for 7–10 days or longer, but few well-controlled studies have evaluated the optimal duration of therapy for patients with CAP, managed in or out of the hospital. Available data on short-course treatment do not suggest any difference in outcome with appropriate therapy in either inpatients or outpatients [276]. Duration is also difficult to define in a uniform fashion, because some antibiotics (such as azithromycin) are administered for a short time yet have a long half-life at respiratory sites of infection.

In trials of antibiotic therapy for CAP, azithromycin has been used for 3–5 days as oral therapy for outpatients, with some reports of single-dose therapy for patients with atypical pathogen infections [276–278]. Results with azithromycin should not be extrapolated to other drugs with significantly shorter half-lives. The ketolide telithromycin has been used for 5–7 days to treat outpatients, including some with pneumococcal bacteremia or PSI classes  $\geq$ III [211]. In a recent study, high-dose (750 mg) levofloxacin therapy for 5 days was equally successful and resulted in more afebrile patients by day 3 than did the 500-mg dose for 7–10 days (49.1% vs. 38.5%;  $P = .03$ ) [276]. On the basis of these studies, 5 days appears to be the minimal overall duration of therapy documented to be effective in usual forms of CAP.

As is discussed above, most patients become clinically stable within 3–7 days, so longer durations of therapy are rarely necessary. Patients with persistent clinical instability are often readmitted to the hospital and may not be candidates for short-duration therapy. Short-duration therapy may be suboptimal

for patients with bacteremic *S. aureus* pneumonia (because of the risk of associated endocarditis and deep-seated infection), for those with meningitis or endocarditis complicating pneumonia, and for those infected with other, less common pathogens (e.g., *Burkholderia pseudomallei* or endemic fungi). An 8-day course of therapy for nosocomial *P. aeruginosa* pneumonia led to relapse more commonly than did a 15-day course of therapy [279]. Whether the same results would be applicable to CAP cases is unclear, but the presence of cavities or other signs of tissue necrosis may warrant prolonged treatment. Studies of duration of therapy have focused on patients receiving empirical treatment, and reliable data defining treatment duration after an initially ineffective regimen are lacking.

### OTHER TREATMENT CONSIDERATIONS

34. Patients with CAP who have persistent septic shock despite adequate fluid resuscitation should be considered for treatment with drotrecogin alfa activated within 24 h of admission. (Weak recommendation, level II evidence.)

Drotrecogin alfa activated is the first immunomodulatory therapy approved for severe sepsis. In the United States, the FDA recommended the use of drotrecogin alfa activated for patients at high risk of death. The high-risk criterion suggested by the FDA was an Acute Physiologic and Chronic Health Assessment (APACHE) II score  $\geq$ 25, based on a subgroup analysis of the overall study. However, the survival advantage (absolute risk reduction, 9.8%) of drotrecogin alfa activated treatment of patients in the CAP subgroup was equivalent to that in the subgroup with APACHE II scores  $\geq$ 25 [92, 280, 281]. The greatest reduction in the mortality rate was for *S. pneumoniae* infection (relative risk, 0.56; 95% CI, 0.35–0.88) [282]. Subsequent data have suggested that the benefit appears to be greatest when the treatment is given as early in the hospital admission as possible. In the subgroup with severe CAP caused by a pathogen other than *S. pneumoniae* and treated with appropriate antibiotics, there was no evidence that drotrecogin alfa activated affected mortality.

Although the benefit of drotrecogin alfa activated is clearly greatest for patients with CAP who have high APACHE II scores, this criterion alone may not be adequate to select appropriate patients. An APACHE II score  $\geq$ 25 was selected by a subgroup analysis of the entire study cohort and may not be similarly calibrated in a CAP-only cohort. Two-organ failure, the criterion suggested for drotrecogin alfa activated use by the European regulatory agency, did not influence the mortality benefit for patients with CAP [92].

Therefore, in addition to patients with septic shock, other patients with severe CAP could be considered for treatment with drotrecogin alfa activated. Those with sepsis-induced leu-

kopenia are at extremely high risk of death and ARDS and are, therefore, potential candidates. Conversely, the benefit of drotrecogin alfa activated is not as clear when respiratory failure is caused more by exacerbation of underlying lung disease rather than by the pneumonia itself. Other minor criteria for severe CAP proposed above are similar to organ failure criteria used in many sepsis trials. Consideration of treatment with drotrecogin alfa activated is appropriate, but the strength of the recommendation is only level II.

35. Hypotensive, fluid-resuscitated patients with severe CAP should be screened for occult adrenal insufficiency. (Moderate recommendation; level II evidence.)

A large, multicenter trial has suggested that stress-dose (200–300 mg of hydrocortisone per day or equivalent) steroid treatment improves outcomes of vasopressor-dependent patients with septic shock who do not have an appropriate cortisol response to stimulation [283]. Once again, patients with CAP made up a significant fraction of patients entered into the trial. In addition, 3 small pilot studies have suggested that there is a benefit to corticosteroid therapy even for patients with severe CAP who are not in shock [284–286]. The small sample size and baseline differences between groups compromise the conclusions. Although the criteria for steroid replacement therapy remain controversial, the frequency of intermittent steroid treatment in patients at risk for severe CAP, such as those with severe COPD, suggests that screening of patients with severe CAP is appropriate with replacement if inadequate cortisol levels are documented. If corticosteroids are used, close attention to tight glucose control is required [287].

36. Patients with hypoxemia or respiratory distress should receive a cautious trial of noninvasive ventilation (NIV) unless they require immediate intubation because of severe hypoxemia (arterial oxygen pressure/fraction of inspired oxygen [ $\text{PaO}_2/\text{FiO}_2$ ] ratio, <150) and bilateral alveolar infiltrates. (Moderate recommendation; level I evidence.)

Patients who do not require immediate intubation but who have either hypoxemia or respiratory distress should receive a trial of NIV [114, 288, 289]. Patients with underlying COPD are most likely to benefit. Patients with CAP who were randomized to receive NIV had a >25% absolute risk reduction for the need for intubation [114]. The use of NIV may also improve intermediate-term mortality. Inability to expectorate may limit the use of NIV [290], but intermittent application of NIV may allow for its use in patients with productive cough unless sputum production is excessive. Prompt recognition of a failed NIV trial is critically important, because most studies

demonstrate worse outcomes for patients who require intubation after a prolonged NIV trial [288, 290]. Within the first 1–2 h of NIV, failure to improve respiratory rate and oxygenation [114, 289, 290] or failure to decrease carbon dioxide partial pressure ( $\text{pCO}_2$ ) in patients with initial hypercarbia [114] predicts NIV failure and warrants prompt intubation. NIV provides no benefit for patients with ARDS [289], which may be nearly indistinguishable from CAP among patients with bilateral alveolar infiltrates. Patients with CAP who have severe hypoxemia ( $\text{PaO}_2/\text{FiO}_2$  ratio, <150) are also poor candidates for NIV [290].

37. Low-tidal-volume ventilation (6  $\text{cm}^3/\text{kg}$  of ideal body weight) should be used for patients undergoing ventilation who have diffuse bilateral pneumonia or ARDS. (Strong recommendation; level I evidence.)

Distinguishing between diffuse bilateral pneumonia and ARDS is difficult, but it may not be an important distinction. Results of the ARDSNet trial suggest that the use of low-tidal-volume ventilation provides a survival advantage [291]. Pneumonia, principally CAP, was the most common cause of ARDS in that trial, and the benefit of the low-tidal-volume ventilatory strategy appeared to be equivalent in the population with pneumonia compared with the entire cohort. The absolute risk reduction for mortality in the pneumonia cohort was 11%, indicating that, in order to avoid 1 death, 9 patients must be treated [292].

Other aspects of the management of severe sepsis and septic shock in patients with CAP do not appear to be significantly different from those for patients with other sources of infection. Recommendations for these aspects of care are reviewed elsewhere [293].

## MANAGEMENT OF NONRESPONDING PNEUMONIA

Because of the limitations of diagnostic testing, the majority of CAP is still treated empirically. Critical to empirical therapy is an understanding of the management of patients who do not follow the normal response pattern.

Although difficult to define, nonresponse is not uncommon. Overall, 6%–15% of hospitalized patients with CAP do not respond to the initial antibiotic treatment [81, 84, 101, 294]. The incidence of treatment failure among patients with CAP who are not hospitalized is not well known, because population-based studies are required. Almirall et al. [295] described an overall hospitalization rate of 60% in a population-based study, but the rate of failure among the 30% of patients who initially presented to their primary care physician was not provided. The frequency of prior antibiotic therapy among Medicare patients admitted to the hospital with CAP is 24%–40%

[95, 109], but the percentage who received prior antibiotic therapy for the acute episode of pneumonia itself versus other indications is unclear. For patients initially admitted to the ICU, the risk of failure to respond is already high; as many as 40% will experience deterioration even after initial stabilization in the ICU [101].

Mortality among nonresponding patients is increased several-fold in comparison with that among responding patients [296]. Overall mortality rates as high as 49% have been reported for an entire population of nonresponding hospitalized patients with CAP [76, 84, 101], and the mortality rate reported in one study of early failure was 27% [81]. APACHE II score was not the only factor independently associated with mortality in the nonresponding group, suggesting that the excess mortality may be due to factors other than severity of illness at presentation [101].

### Definition and classification.

38. The use of a systematic classification of possible causes of failure to respond, based on time of onset and type of failure (table 11), is recommended. (Moderate recommendation; level II evidence.)

The term “nonresponding pneumonia” is used to define a situation in which an inadequate clinical response is present despite antibiotic treatment. Lack of a clear-cut and validated definition in the literature makes nonresponse difficult to study. Lack of response also varies according to the site of treatment. Lack of response in outpatients is very different from that in patients admitted to the ICU. The time of evaluation is also important. Persistent fever after the first day of treatment differs significantly from fever persisting (or recurring) at day 7 of treatment.

Table 11 provides a construct for evaluating nonresponse to antibiotic treatment of CAP, based on several studies addressing this issue [76, 81, 84, 101]. Two patterns of unacceptable response are seen in hospitalized patients [101]. The first is progressive pneumonia or actual clinical deterioration, with acute respiratory failure requiring ventilatory support and/or septic shock, usually occurring within the first 72 h of hospital admission. As is noted above, as many as 45% of patients with CAP who ultimately require ICU admission are initially admitted to a non-ICU setting and are transferred because of deterioration [75]. Deterioration and development of respiratory failure or hypotension >72 h after initial treatment is often related to intercurrent complications, deterioration in underlying disease, or development of nosocomial superinfection.

The second pattern is that of persistent or nonresponding pneumonia. Nonresponse can be defined as absence of or delay in achieving clinical stability, using the criteria in table 10 [274, 294]. When these criteria were used, the median time to achieve

**Table 11. Patterns and etiologies of types of failure to respond.**

Failure to improve
Early (<72 h of treatment)
Normal response
Delayed
Resistant microorganism
Uncovered pathogen
Inappropriate by sensitivity
Parapneumonic effusion/empyema
Nosocomial superinfection
Nosocomial pneumonia
Extrapulmonary
Noninfectious
Complication of pneumonia (e.g., BOOP)
Misdiagnosis: PE, CHF, vasculitis
Drug fever
Deterioration or progression
Early (<72 h of treatment)
Severity of illness at presentation
Resistant microorganism
Uncovered pathogen
Inappropriate by sensitivity
Metastatic infection
Empyema/parapneumonic
Endocarditis, meningitis, arthritis
Inaccurate diagnosis
PE, aspiration, ARDS
Vasculitis (e.g., SLE)
Delayed
Nosocomial superinfection
Nosocomial pneumonia
Extrapulmonary
Exacerbation of comorbid illness
Intercurrent noninfectious disease
PE
Myocardial infarction
Renal failure

**NOTE.** ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia; CHF, congestive heart failure; PE, pulmonary embolus; SLE, systemic lupus erythematosus.

clinical stability was 3 days for all patients, but a quarter of patients took  $\geq 6$  days to meet all of these criteria for stability [274]. Stricter definitions for each of the criteria and higher PSI scores were associated with longer times to achieve clinical stability. Conversely, subsequent transfer to the ICU after achieving this degree of clinical stability occurred in <1% of cases. A separate multicenter trial demonstrated similar findings [297]. Given these results, concern regarding nonresponse should be tempered before 72 h of therapy. Antibiotic changes during this period should be considered only for patients with deterioration or in whom new culture data or epidemiologic clues suggest alternative etiologies.

Finally, nonresolving or slow-resolving pneumonia has been

used to refer to the conditions of patients who present with persistence of pulmonary infiltrates >30 days after initial pneumonia-like syndrome [298]. As many as 20% of these patients will be found to have diseases other than CAP when carefully evaluated [295].

Two studies have evaluated the risk factors for a lack of response in multivariate analyses [81, 84], including those amenable to medical intervention. Use of fluoroquinolones was independently associated with a better response in one study [84], whereas discordant antimicrobial therapy was associated with early failure [81]. In table 12, the different risk and protective factors and their respective odds ratios are summarized.

Specific causes that may be responsible for a lack of response in CAP have been classified by Arancibia et al. [101] (table 11). This classification may be useful for clinicians as a systematic approach to diagnose the potential causes of nonresponse in CAP. Although in the original study only 8 (16%) of 49 cases could not be classified [101], a subsequent prospective multicenter trial found that the cause of failure could not be determined in 44% [84].

**Management of nonresponding CAP.** Nonresponse to antibiotics in CAP will generally result in  $\geq 1$  of 3 clinical responses: (1) transfer of the patient to a higher level of care, (2) further diagnostic testing, and (3) escalation or change in treatment. Issues regarding hospital admission and ICU transfer are discussed above.

An inadequate host response, rather than inappropriate antibiotic therapy or unexpected microorganisms, is the most common cause of apparent antibiotic failure when guideline-recommended therapy is used. Decisions regarding further di-

agnostic testing and antibiotic change/escalation are intimately intertwined and need to be discussed in tandem.

Information regarding the utility of extensive microbiological testing in cases of nonresponding CAP is mainly retrospective and therefore affected by selection bias. A systematic diagnostic approach, which included invasive, noninvasive, and imaging procedures, in a series of nonresponding patients with CAP obtained a specific diagnosis in 73% [101]. In a different study, mortality among patients with microbiologically guided versus empirical antibiotic changes was not improved (mortality rate, 67% vs. 64%, respectively) [76]. However, no antibiotic changes were based solely on sputum smears, suggesting that invasive cultures or nonculture methods may be needed.

Mismatch between the susceptibility of a common causative organism, infection with a pathogen not covered by the usual empirical regimen, and nosocomial superinfection pneumonia are major causes of apparent antibiotic failure. Therefore, the first response to nonresponse or deterioration is to reevaluate the initial microbiological results. Culture or sensitivity data not available at admission may now make the cause of clinical failure obvious. In addition, a further history of any risk factors for infection with unusual microorganisms (table 8) should be taken if not done previously. Viruses are relatively neglected as a cause of infection in adults but may account for 10%–20% of cases [299]. Other family members or coworkers may have developed viral symptoms in the interval since the patient was admitted, increasing suspicion of this cause.

The evaluation of nonresponse is severely hampered if a microbiological diagnosis was not made on initial presentation. If cultures were not obtained, clinical decisions are much more

**Table 12. Factors associated with nonresponding pneumonia.**

Risk factor	Overall failure <sup>a</sup>		Early failure <sup>b</sup>	
	Decreased risk	Increased risk	Decreased risk	Increased risk
Older age (>65 years)	...	...	0.35	...
COPD	0.60	...	...	...
Liver disease	...	2.0	...	...
Vaccination	0.3	...	...	...
Pleural effusion	...	2.7	...	...
Multilobar infiltrates	...	2.1	...	1.81
Cavitation	...	4.1	...	...
Leukopenia	...	3.7	...	...
PSI class	...	1.3	...	2.75
<i>Legionella</i> pneumonia	...	...	...	2.71
Gram-negative pneumonia	...	...	...	4.34
Fluoroquinolone therapy	0.5	...	...	...
Concordant therapy	...	...	0.61	...
Discordant therapy	...	...	...	2.51

**NOTE.** Data are relative risk values. COPD, chronic obstructive pulmonary disease; PSI, Pneumonia Severity Index.

<sup>a</sup> From [84].

<sup>b</sup> From [81].

difficult than if the adequate cultures were obtained but negative. Risk factors for nonresponse or deterioration (table 12), therefore, figure prominently in the list of situations in which more aggressive initial diagnostic testing is warranted (table 5).

Blood cultures should be repeated for deterioration or progressive pneumonia. Deteriorating patients have many of the risk factors for bacteremia, and blood cultures are still high yield even in the face of prior antibiotic therapy [95]. Positive blood culture results in the face of what should be adequate antibiotic therapy should increase the suspicion of either antibiotic-resistant isolates or metastatic sites, such as endocarditis or arthritis.

Despite the high frequency of infectious pulmonary causes of nonresponse, the diagnostic utility of respiratory tract cultures is less clear. Caution in the interpretation of sputum or tracheal aspirate cultures, especially of gram-negative bacilli, is warranted because early colonization, rather than superinfection with resistant bacteria, is not uncommon in specimens obtained after initiation of antibiotic treatment. Once again, the absence of multidrug-resistant pathogens, such as MRSA or *Pseudomonas*, is strong evidence that they are not the cause of nonresponse. An etiology was determined by bronchoscopy in 44% of patients with CAP, mainly in those not responding to therapy [300]. Despite the potential benefit suggested by these results, and in contrast to ventilator-associated pneumonia [301, 302], no randomized study has compared the utility of invasive versus noninvasive strategies in the CAP population with nonresponse.

Rapid urinary antigen tests for *S. pneumoniae* and *L. pneumophila* remain positive for days after initiation of antibiotic therapy [147, 152] and, therefore, may be high-yield tests in this group. A urinary antigen test result that is positive for *L. pneumophila* has several clinical implications, including that coverage for *Legionella* should be added if not started empirically [81]. This finding may be a partial explanation for the finding that fluoroquinolones are associated with a lower incidence of nonresponse [84]. If a patient has persistent fever, the faster response to fluoroquinolones in *Legionella* CAP warrants consideration of switching coverage from a macrolide [303]. Stopping the  $\beta$ -lactam component of combination therapy to exclude drug fever is probably also safe [156]. Because one of the major explanations for nonresponse is poor host immunity rather than incorrect antibiotics, a positive pneumococcal antigen test result would at least clarify the probable original pathogen and turn attention to other causes of failure. In addition, a positive pneumococcal antigen test result would also help with interpretation of subsequent sputum/tracheal aspirate cultures, which may indicate early superinfection.

Nonresponse may also be mimicked by concomitant or subsequent extrapulmonary infection, such as intravascular catheter, urinary, abdominal, and skin infections, particularly in

ICU patients. Appropriate cultures of these sites should be considered for patients with nonresponse to CAP therapy.

In addition to microbiological diagnostic procedures, several other tests appear to be valuable for selected patients with nonresponse:

- Chest CT. In addition to ruling out pulmonary emboli, a CT scan can disclose other reasons for antibiotic failure, including pleural effusions, lung abscess, or central airway obstruction. The pattern of opacities may also suggest alternative noninfectious disease, such as bronchiolitis obliterans organizing pneumonia.
- Thoracentesis. Empyema and parapneumonic effusions are important causes of nonresponse [81, 101], and thoracentesis should be performed whenever significant pleural fluid is present.
- Bronchoscopy with BAL and transbronchial biopsies. If the differential of nonresponse includes noninfectious pneumonia mimics, bronchoscopy will provide more diagnostic information than routine microbiological cultures. BAL may reveal noninfectious entities, such as pulmonary hemorrhage or acute eosinophilic pneumonia, or hints of infectious diseases, such as lymphocytic rather than neutrophilic alveolitis pointing toward virus or *Chlamydomphila* infection. Transbronchial biopsies can also yield a specific diagnosis.

Antibiotic management of nonresponse in CAP has not been studied. The overwhelming majority of cases of apparent nonresponse are due to the severity of illness at presentation or a delay in treatment response related to host factors. Other than the use of combination therapy for severe bacteremic pneumococcal pneumonia [112, 231, 233, 234], there is no documentation that additional antibiotics for early deterioration lead to a better outcome. The presence of risk factors for potentially untreated microorganisms may warrant temporary empirical broadening of the antibiotic regimen until results of diagnostic tests are available.

## PREVENTION

39. All persons  $\geq 50$  years of age, others at risk for influenza complications, household contacts of high-risk persons, and health care workers should receive inactivated influenza vaccine as recommended by the Advisory Committee on Immunization Practices (ACIP), CDC. (Strong recommendation; level I evidence.)
40. The intranasally administered live attenuated vaccine is an alternative vaccine formulation for some persons 5–49 years of age without chronic underlying diseases, including immunodeficiency, asthma, or chronic medical conditions. (Strong recommendation; level I evidence.)
41. Health care workers in inpatient and outpatient settings and long-term care facilities should receive annual in-

**Table 13. Recommendations for vaccine prevention of community-acquired pneumonia.**

Factor	Pneumococcal polysaccharide vaccine	Inactivated influenza vaccine	Live attenuated influenza vaccine
Route of administration	Intramuscular injection	Intramuscular injection	Intranasal spray
Type of vaccine	Bacterial component (polysaccharide capsule)	Killed virus	Live virus
Recommended groups	All persons ≥65 years of age  High-risk persons 2–64 years of age Current smokers <sup>b</sup>	All persons ≥50 years of age  High-risk persons 6 months–49 years of age Household contacts of high-risk persons Health care providers Children 6–23 months of age	Healthy persons 5–49 years of age, <sup>a</sup> including health care providers and household contacts of high-risk persons
Specific high-risk indications for vaccination	Chronic cardiovascular, pulmonary, renal, or liver disease  Diabetes mellitus  Cerebrospinal fluid leaks Alcoholism Asplenia  Immunocompromising conditions/medications Native Americans and Alaska natives Long-term care facility residents	Chronic cardiovascular or pulmonary disease (including asthma)  Chronic metabolic disease (including diabetes mellitus)  Renal dysfunction Hemoglobinopathies Immunocompromising conditions/medications Compromised respiratory function or increased aspiration risk Pregnancy  Residence in a long-term care facility Aspirin therapy in persons ≤18 years of age	Avoid in high-risk persons
Revaccination schedule	One-time revaccination after 5 years for (1) adults ≥65 years of age, if the first dose is received before age 65 years; (2) persons with asplenia; and (3) immunocompromised persons	Annual revaccination	Annual revaccination

**NOTE.** Adapted from the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention [304].

<sup>a</sup> Avoid use in persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including diabetes, renal dysfunction, and hemoglobinopathies; persons with immunodeficiencies or who receive immunosuppressive therapy; children or adolescents receiving salicylates; persons with a history of Guillain-Barré syndrome; and pregnant women.

<sup>b</sup> Vaccinating current smokers is recommended by the Pneumonia Guidelines Committee but is not currently an indication for vaccine according to the Advisory Committee on Immunization Practices statement.

influenza immunization. (Strong recommendation; level I evidence.)

- Pneumococcal polysaccharide vaccine is recommended for persons ≥65 years of age and for those with selected high-risk concurrent diseases, according to current ACIP guidelines. (Strong recommendation; level II evidence.)

Vaccines targeting pneumococcal disease and influenza remain the mainstay for preventing CAP. Pneumococcal polysaccharide vaccine and inactivated influenza vaccine are recommended for all older adults and for younger persons with

medical conditions that place them at high risk for pneumonia morbidity and mortality (table 13) [304, 305]. The new live attenuated influenza vaccine is recommended for healthy persons 5–49 years of age, including health care workers [304].

Postlicensure epidemiologic studies have documented the effectiveness of pneumococcal polysaccharide vaccines for prevention of invasive infection (bacteremia and meningitis) among elderly individuals and younger adults with certain chronic medical conditions [306–309]. The overall effectiveness against invasive pneumococcal disease among persons ≥65 years of age is 44%–75% [306, 308, 310], although efficacy may

decrease with advancing age [308]. The effectiveness of the vaccine against pneumococcal disease in immunocompromised persons is less clear, and results of studies evaluating its effectiveness against pneumonia without bacteremia have been mixed. The vaccine has been shown to be cost effective for general populations of adults 50–64 years of age and  $\geq 65$  years of age [311, 312]. A second dose of pneumococcal polysaccharide vaccine after a  $\geq 5$ -year interval has been shown to be safe, with only slightly more local reactions than are seen after the first dose [313]. Because the safety of a third dose has not been demonstrated, current guidelines do not suggest repeated revaccination. The pneumococcal conjugate vaccine is under investigation for use in adults but is currently only licensed for use in young children [314, 315]. However, its use in children  $< 5$  years of age has dramatically reduced invasive pneumococcal bacteremia among adults as well [314, 316].

The effectiveness of influenza vaccines depends on host factors and on how closely the antigens in the vaccine are matched with the circulating strain of influenza. A systematic review demonstrates that influenza vaccine effectively prevents pneumonia, hospitalization, and death [317, 318]. A recent large observational study of adults  $\geq 65$  years of age found that vaccination against influenza was associated with a reduction in the risk of hospitalization for cardiac disease (19% reduction), cerebrovascular disease (16%–23% reduction), and pneumonia or influenza (29%–32% reduction) and a reduction in the risk of death from all causes (48%–50% reduction) [319]. In long-term-care facilities, vaccination of health care workers with influenza vaccine is an important preventive health measure [318, 320, 321]. Because the main virulence factors of influenza virus, a neuraminidase and hemagglutinin, adapt quickly to selective pressures, new vaccine formulations are created each year on the basis of the strains expected to be circulating, and annual revaccination is needed for optimal protection.

43. Vaccination status should be assessed at the time of hospital admission for all patients, especially those with medical illnesses. (Moderate recommendation; level III evidence.)
44. Vaccination may be performed either at hospital discharge or during outpatient treatment. (Moderate recommendation; level III evidence.)
45. Influenza vaccine should be offered to persons at hospital discharge or during outpatient treatment during the fall and winter. (Strong recommendation; level III evidence.)

Many people who should receive either influenza or pneumococcal polysaccharide vaccine have not received them. According to a 2003 survey, only 69% of adults  $\geq 65$  years of age had received influenza vaccine in the past year, and only 64% had ever received pneumococcal polysaccharide vaccine [322].

Coverage levels are lower for younger persons with vaccine indications. Among adults 18–64 years of age with diabetes, 49% had received influenza vaccine, and 37% had ever received pneumococcal vaccine [323]. Studies of vaccine delivery methods indicate that the use of standing orders is the best way to improve vaccination coverage in office, hospital, or long-term care settings [324].

Hospitalization of at-risk patients represents an underutilized opportunity to assess vaccination status and to either provide or recommend immunization. Ideally, patients should be vaccinated before developing pneumonia; therefore, admissions for illnesses other than respiratory tract infections would be an appropriate focus. However, admission for pneumonia is an important trigger for assessing the need for immunization. The actual immunization may be better provided at the time of outpatient follow-up, especially with the emphasis on early discharge of patients with CAP. Patients with an acute fever should not be vaccinated until their fever has resolved. Confusion of a febrile reaction to immunization with recurrent/superinfection pneumonia is a risk. However, immunization at discharge for pneumonia is warranted for patients for whom outpatient follow-up is unreliable, and such vaccinations have been safely given to many patients.

The best time for influenza vaccination in North America is October and November, although vaccination in December and later is recommended for those who were not vaccinated earlier. Influenza and pneumococcal vaccines can be given at the same time in different arms.

Chemoprophylaxis can be used as an adjunct to vaccination for prevention and control of influenza. Oseltamivir and zanamivir are both approved for prophylaxis; amantadine and rimantadine have FDA indications for chemoprophylaxis against influenza A infection, but these agents are currently not recommended because of the frequency of resistance among strains circulating in the United States and Canada [252, 253]. Developing an adequate immune response to the inactivated influenza vaccine takes  $\sim 2$  weeks in adults; chemoprophylaxis may be useful during this period for those with household exposure to influenza, those who live or work in institutions with an influenza outbreak, or those who are at high risk for influenza complications in the setting of a community outbreak [325, 326]. Chemoprophylaxis also may be useful for persons with contraindications to influenza vaccine or as an adjunct to vaccination for those who may not respond well to influenza vaccine (e.g., persons with HIV infection) [325, 326]. The use of influenza antiviral medications for treatment or chemoprophylaxis should not affect the response to the inactivated vaccine. Because it is unknown whether administering influenza antiviral medications affects the performance of the new live attenuated intranasal vaccine, this vaccine should not be used in conjunction with antiviral agents.

Other types of vaccination can be considered. Pertussis is a rare cause of pneumonia itself. However, pneumonia is one of the major complications of pertussis. Concern over waning immunity has led the ACIP to emphasize adult immunization for pertussis [327]. One-time vaccination with the new tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine—adsorbed (Tdap) product, ADACEL (Sanofi Pasteur)—is recommended for adults 19–64 years of age. For most adults, the vaccine should be given in place of their next routine tetanus-diphtheria booster; adults with close contact with infants <12 months of age and health care workers should receive the vaccine as soon as possible, with an interval as short as 2 years after their most recent tetanus/diphtheria booster.

46. Smoking cessation should be a goal for persons hospitalized with CAP who smoke. (Moderate recommendation; level III evidence.)
47. Smokers who will not quit should also be vaccinated for both pneumococcus and influenza. (Weak recommendation; level III evidence.)

Smoking is associated with a substantial risk of pneumococcal bacteremia; one report showed that smoking was the strongest of multiple risks for invasive pneumococcal disease in immunocompetent nonelderly adults [328]. Smoking has also been identified as a risk for *Legionella* infection [329]. Smoking cessation should be attempted when smokers are hospitalized; this is particularly important and relevant when these patients are hospitalized for pneumonia. Materials for clinicians and patients to assist with smoking cessation are available online from the US Surgeon General (<http://www.surgeongeneral.gov/tobacco>), the Centers for Disease Control and Prevention (<http://www.cdc.gov/tobacco>), and the American Cancer Society (<http://www.cancer.org>). The most successful approaches to quitting include some combination of nicotine replacement and/or bupropion, a method to change habits, and emotional support. Given the increased risk of pneumonia, the committee felt that persons unwilling to stop smoking should be given the pneumococcal polysaccharide vaccine, although this is not currently an ACIP-recommended indication.

48. Cases of pneumonia that are of public health concern should be reported immediately to the state or local health department. (Strong recommendation; level III evidence.)

Public health interventions are important for preventing some forms of pneumonia. Notifying the state or local health department about a condition of interest is the first step to getting public health professionals involved. Rules and regulations regarding which diseases are reportable differ between

states. For pneumonia, most states require reporting for legionnaires disease, SARS, and psittacosis, so that an investigation can determine whether others may be at risk and whether control measures are necessary. For legionnaires disease, reporting of cases has helped to identify common-source outbreaks caused by environmental contamination [130]. For SARS, close observation and, in some cases, quarantine of close contacts have been critical for controlling transmission [330]. In addition, any time avian influenza (H5N1) or a possible terrorism agent (e.g., plague, tularemia, or anthrax) is being considered as the etiology of pneumonia, the case should be reported immediately, even before a definitive diagnosis is obtained. In addition, pneumonia cases that are caused by pathogens not thought to be endemic to the area should be reported, even if those conditions are not typically on the list of reportable conditions, because control strategies might be possible.

For other respiratory diseases, episodes that are suspected of being part of an outbreak or cluster should be reported. For pneumococcal disease and influenza, outbreaks can occur in crowded settings of susceptible hosts, such as homeless shelters, nursing homes, and jails. In these settings, prophylaxis, vaccination, and infection control methods are used to control further transmission [331]. For *Mycoplasma*, antibiotic prophylaxis has been used in schools and institutions to control outbreaks [332].

49. Respiratory hygiene measures, including the use of hand hygiene and masks or tissues for patients with cough, should be used in outpatient settings and EDs as a means to reduce the spread of respiratory infections. (Strong recommendation; level III evidence.)

In part because of the emergence of SARS, improved respiratory hygiene measures (“respiratory hygiene” or “cough etiquette”) have been promoted as a means for reducing transmission of respiratory infections in outpatient clinics and EDs [333]. Key components of respiratory hygiene include encouraging patients to alert providers when they present for a visit and have symptoms of a respiratory infection; the use of hand hygiene measures, such as alcohol-based hand gels; and the use of masks or tissues to cover the mouth for patients with respiratory illnesses. In a survey of the US population, the use of masks in outpatient settings was viewed as an acceptable means for reducing the spread of respiratory infections [334]. For hospitalized patients, infection control recommendations typically are pathogen specific. For more details on the use of personal protective equipment and other measures to prevent transmission within health care settings, refer to the Healthcare Infection Control Practices Advisory Committee [335].

## SUGGESTED PERFORMANCE INDICATORS

Performance indicators are tools to help guideline users measure both the extent and the effects of implementation of guidelines. Such tools or measures can be indicators of the process itself, outcomes, or both. Deviations from the recommendations are expected in a proportion of cases, and compliance in 80%–95% of cases is generally appropriate, depending on the indicator.

Four specific performance indicators have been selected for the CAP guidelines, 3 of which focus on treatment issues and 1 of which deals with prevention:

- Initial empirical treatment of CAP should be consistent with guideline recommendations. Data exist that support the role of CAP guidelines and that have demonstrated reductions in cost, LOS, and mortality when the guidelines are followed. Reasons for deviation from the guidelines should be clearly documented in the medical record.
- The first treatment dose for patients who are to be admitted to the hospital should be given in the ED. Unlike in prior guidelines, a specific time frame is not being recommended. Initiation of treatment would be expected within 6–8 h of presentation whenever the admission diagnosis is likely CAP. A rush to treatment without a diagnosis of CAP can, however, result in the inappropriate use of antibiotics with a concomitant increase in costs, adverse drug events, increased antibiotic selection pressure, and, possibly, increased antibiotic resistance. Consideration should be given to monitoring the number of patients who receive empirical antibiotics in the ED but are admitted to the hospital without an infectious diagnosis.
- Mortality data for all patients with CAP admitted to wards, ICUs, or high-level monitoring units should be collected. Although tools to predict mortality and severity of illness exist—such as the PSI and CURB-65 criteria, respectively—none is foolproof. Overall mortality rates for all patients with CAP admitted to the hospital, including general medical wards, should be monitored and compared with severity-adjusted norms. In addition, careful attention should be paid to the percentage of patients with severe CAP, as defined in this document, who are admitted initially to a non-ICU or a high-level monitoring unit and to their mortality rate.
- It is important to determine what percentage of at-risk patients in one's practice actually receive immunization for influenza or pneumococcal infection. Prevention of infection is clearly more desirable than having to treat established infection, but it is clear that target groups are undervaccinated. Trying to increase the number of protected individuals is a desirable end point and, therefore, a goal worth pursuing. This is particularly true for influenza, because the vaccine data are more compelling, but it is important to try

to protect against pneumococcal infection as well. Coverage of 90% of adults  $\geq 65$  years of age should be the target.

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