American Thoracic Society

Guidelines for the Management of Adults with Community-acquired Pneumonia

Diagnosis, Assessment of Severity, Antimicrobial Therapy, and Prevention

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS MARCH 9, 2001

EXECUTIVE SUMMARY

This document is an update of the original 1993 statement on community-acquired pneumonia, incorporating new information about bacteriology, patient stratification, diagnostic evaluation, antibiotic therapy, and prevention. The statement includes a summary of the available literature, as well as evidence-based recommendations for patient management, developed by a multidisciplinary group composed of pulmonary, critical care, general internal medicine, and infectious disease specialists.

The sections of this document are as follows: an overview of the purpose of our efforts and the methodology used to collect and grade the available data; a review of the likely etiologic pathogens causing community-acquired pneumonia (CAP), including a discussion of drug-resistant *Streptococcus pneumoniae* (DRSP); a proposed approach to patient stratification for the purpose of predicting the likely etiologic pathogens of different patient populations with CAP; a summary of available and recommended diagnostic studies; suggestions on how to define the need for hospitalization and admission to the intensive care unit (ICU) for patients with CAP; guidelines for antibiotic therapy of CAP, including principles of therapy and specific recommendations for each patient category; an approach to the nonresponding patient, as well as a discussion of when to switch to oral therapy and when to discharge an admitted patient with CAP who is responding to initial therapy; and recommendations for the use of pneumococcal and influenza vaccines.

Likely Pathogens and Patient Stratification

All CAP patients fall into one of four groups, each with a list of likely pathogens, and suggested empiric therapy follows from this list (*see* Figure 1). Stratification is based on an assessment of place of therapy (outpatient, inpatient ward, or intensive care unit), the presence of cardiopulmonary disease, and the presence of "modifying factors" (*see* Table 1), which include risk factors for DRSP, enteric gram-negatives, and *Pseudomonas aeruginosa.* Not every patient should be considered as being at risk for infection with DRSP, and clinical risk factors have been defined. The role of enteric gram-negatives in CAP is controversial, but these organisms do not need to be considered unless specific risk factors are present; however, one of these risk factors includes residence in a nursing home, a population that is not excluded from this statement.

For all patients with CAP, pneumococcus is the most common pathogen, and may even account for pneumonia in patients who have no pathogen identified by routine diagnostic testing. Although the incidence of DRSP is increasing, available data show that mortality in CAP is adversely affected by drug-resistant pneumococci only when minimal inhibitory concentration (MIC) values to penicillin are $\geq$ 4 mg/L. The impact of organisms at lower levels of resistance remains uncertain. All patients with CAP could potentially be infected with *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* spp. (the "atypical" pathogens), either alone or as part of a mixed infection, and thus all patients should receive therapy to account for this possibility. Although the term "atypical pneumonia" is not an accurate description of the clinical features of CAP, the use of the term "atypical" was retained in this statement to refer to the specific pathogens listed above. When patients with CAP are admitted to the ICU, the organisms responsible include pneumococcus, the "atypical" pathogens (especially *Legionella* in some series), and enteric gram-negatives. *Pseudomonas aeruginosa* has been recovered from some patients with severe CAP, but this organism should be considered only when patients have well-identified risk factors present.

Diagnostic Testing

All patients with CAP should have a chest radiograph to establish the diagnosis and the presence of complications (pleural effusion, multilobar disease), although in some outpatient settings, this may be impossible. All outpatients should have a careful assessment of disease severity, but sputum culture and Gram's stain are not required. All admitted patients with CAP should have an assessment of gas exchange (oximetry or arterial blood gas), routine blood chemistry and blood counts, and a collection of two sets of blood cultures. If a drug-resistant pathogen, or an organism not covered by usual empiric therapy, is suspected, sputum culture should be obtained, and Gram's stain should be used to guide interpretation of culture results. In general, sputum Gram's stain cannot be used to focus initial empiric antibiotic therapy, but could be used to broaden initial antibiotic therapy to include organisms found on the Gram's stain that are not covered by the usual initial empiric antibiotic therapy options. Routine serologic testing is not recommended for any population with CAP. For patients with severe CAP, *Legionella* urinary antigen should be measured, and aggressive efforts at establishing an etiologic diagnosis should be made, including the collection of bronchoscopic samples of lower respiratory secretions in selected patients, although the benefit of such efforts has not been proven.

Admission Decision and Need for ICU Care

The admission decision remains an "art of medicine" decision, and prognostic scoring rules (the Pneumonia Patient Out-

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comes Research Team [PORT] and British Thoracic Society rules), are adjunctive tools to support, but not replace, this process. In general, hospitalization is needed if patients have multiple risk factors for a complicated course, and these are summarized in this document. Patients may also need to be hospitalized for a variety of nonmedical reasons, and such social factors should also be incorporated into the admission decision process.

Admission to the ICU is needed for patients with severe CAP, defined as the presence of either one of two major criteria, or the presence of two of three minor criteria. The major criteria include need for mechanical ventilation and septic shock; the minor criteria include systolic blood pressure (BP) $\leq$ 90 mm Hg, multilobar disease, and Pa_{O_2}/FI_{O_2} ratio $<$ 250. Patients who have two of four criteria from the British Thoracic Society rules also have more severe illness and should be considered for ICU admission. These criteria include respiratory rate $\geq$ 30/min, diastolic blood pressure $\leq$ 60 mm Hg, blood urea nitrogen (BUN) $>$ 7.0 mM ($>$ 19.1 mg/dl), and confusion.

Therapy Principles and Recommendations

Patients should initially be treated empirically, based on the likely pathogens for each of the four patient groups (*see* Tables 2–5), although when culture results become available, organism-specific therapy may be possible for some patients. All populations should be treated for the possibility of atypical pathogen infection, and this should be with a macrolide (or tetracycline) alone in outpatients, or an intravenous macrolide alone in inpatients who have no risk factors for DRSP, gram-negatives, or aspiration. For outpatients or non-ICU inpatients with risk factors for these other organisms, therapy should be with either a β-lactam/macrolide combination or an antipneumococcal fluoroquinolone alone. Although both regimens appear therapeutically equivalent, particularly among inpatients, in the outpatient treatment of the more complicated patient, an antipneumococcal fluoroquinolone may be more convenient than a β-lactam/macrolide combination. All admitted patients should receive their first dose of antibiotic therapy within 8 h of arrival to the hospital. In the ICU-admitted patient, current data do not support the use of an antipneumococcal fluoroquinolone alone, and therapy should be with a β-lactam plus either a macrolide or quinolone, using a regimen with two antipseudomonal agents in appropriate, at-risk, patients.

If a β-lactam/macrolide combination is used for a patient with risk factors for DRSP, only selected β-lactams can be used, and these include oral therapy with cefpodoxime, amoxicillin/clavulanate, high-dose amoxicillin, or cefuroxime; or intravenous therapy with ceftriaxone, cefotaxime, ampicillin/sulbactam, or high-dose ampicillin. Ceftriaxone can also be given intramuscularly. There are several antibiotics, such as cefepime, imipenem, meropenem, and piperacillin/tazobactam that are generally clinically active against DRSP, but since these agents are also active against *P. aeruginosa*, they should be reserved for patients with risk factors for this organism.

Clinical Response, Switch to Oral Therapy, and Discharge

Most patients with CAP will have an adequate clinical response within 3 d, and when the patient has met appropriate criteria, switch to oral therapy should be made. Criteria for switch include improvement in cough and dyspnea; afebrile ($<$ 100° F) on two occasions 8 h apart; white blood cell count decreasing; and functioning gastrointestinal tract with adequate oral intake. Even if the patient is febrile, switch therapy can occur, if other clinical features are favorable. If the patient has met criteria for switch, oral therapy can be started and the patient discharged on the same day, if other medical and social factors permit.

For most patients, initial antibiotic therapy should not be changed in the first 72 h, unless there is a marked clinical deterioration. Up to 10% of all CAP patients will not respond to initial therapy, and a diagnostic evaluation is necessary to look for a drug-resistant or unusual (or unsuspected) pathogen, a nonpneumonia diagnosis (inflammatory disease or pulmonary embolus), or a pneumonia complication. This evaluation begins with a careful requestioning about epidemiologic factors that predispose to specific pathogens (*see* Table 6).

Prevention

Pneumonia can be prevented by the use of pneumococcal and influenza vaccines in appropriate at-risk populations. Smoking cessation should be promoted in all patients, and can also eliminate an important risk factor for CAP.

INTRODUCTION

Community-acquired pneumonia (CAP) remains a common and serious illness, in spite of the availability of potent new antimicrobials and effective vaccines. In the United States, pneumonia is the sixth leading cause of death, and the number one cause of death from infectious diseases (1, 2). Because pneumonia is not a reportable illness, information about its incidence is based on crude estimates, but it appears that up to 5.6 million cases of community-acquired pneumonia occur annually, and as many as 1.1 million of these require hospitalization (1, 2). In the outpatient setting, the mortality rate of pneumonia remains low, in the range of $<$ 1–5%, but among patients with community-acquired pneumonia who require hospitalization, the mortality rate averages 12% overall, but increases in specific populations, such as those with bacteremia, and those from nursing home settings, and approaches 40% in those who are most ill and who require admission to the intensive care unit (3–26).

Both the epidemiology and treatment of pneumonia have undergone changes. Pneumonia is increasingly being recognized among older patients and those with comorbidity (coexisting illness) (2, 15, 18, 19, 21). Such illnesses include chronic obstructive lung disease, diabetes mellitus, renal insufficiency, congestive heart failure, coronary artery disease, malignancy, chronic neurologic disease, and chronic liver disease (15). These individuals may become infected with a variety of newly identified, or previously unrecognized, pathogens (5, 14, 17, 27–32). At the same time, a number of new antimicrobial agents have become available, some with utility for community-acquired pneumonia. Paralleling the improvement in our antibiotic armamentarium has been the evolution of bacterial resistance mechanisms. In the 1990s, many of the common respiratory pathogens have become resistant, *in vitro*, to widely used antimicrobials. Resistance, by a variety of mechanisms, is being identified with increasing frequency among *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis*, and a number of enteric gram-negative bacteria (33–39).

Chronic obstructive pulmonary disease (COPD) is a common illness, affecting up to 15 million persons in the United States, with more than 12 million having a component of illness characterized as chronic bronchitis, and these patients commonly develop community-acquired respiratory infections, including pneumonia (40). COPD is the fourth leading cause of death in the United States, and age-adjusted death rates in this illness have risen, whereas other common causes of death such as heart disease and cerebral vascular disease have fallen (40–

42). This population is prone to frequent acute bronchitic exacerbations of chronic bronchitis (AECB), and bacterial infection is believed to play a role in at least half of these episodes (43). Although most experts agree that antibiotics should not be used in patients with acute bronchitis in the absence of chronic lung disease, the role of antibiotic therapy in AECB is controversial, with some patients receiving such therapy and others not. At the current time, the role of antibiotic therapy in this illness is uncertain, and it remains unclear whether specific subpopulations of patients with AECB can be defined for the purpose of prescribing different therapy to different patients.

In 1993, the American Thoracic Society (ATS) published guidelines for the initial management of community-acquired pneumonia, based on available knowledge and a consensus of experts (44). Since that time, new information has become available in many areas related to this illness, including prognostic scoring to predict mortality, new knowledge of the bacteriology of this illness, and new approaches to providing care in a cost-effective and efficient manner. Since 1993, a number of new antibiotics have been approved for the therapy of CAP, in at least four different drug classes. At the same time, *in vitro* antibiotic resistance among the organisms causing CAP has become increasingly prevalent, and the clinical relevance of resistance is beginning to be understood.

Goals of This Document

This document is a revision of the initial CAP guidelines, intended to update and expand on the original statement, by including more recent information as well as by covering new areas such as pneumonia prevention and the importance of drug-resistant organisms. It includes not only elements from the original ATS CAP guidelines, but also takes into account the recommendations from the more recently published guidelines of the Infectious Diseases Society of America (IDSA, Alexandria, VA) and the newly published Canadian CAP document (45, 46). The discussion is limited to the apparently immunocompetent patient with community-acquired pneumonia, because this represents the population most commonly encountered. However, patients with immune suppression due to chronic corticosteroid therapy and due to nonhematologic malignancy (without neutropenia) are commonly treated by many types of physicians, and the approach to these patients is included in this document. The approach to other immunocompromised patients is different, because of the large number of potential etiologic agents for pneumonia in these individuals. Thus the discussion does not deal with the problems of pneumonia in the human immunodeficiency virus (HIV)-infected patient, or in those immunocompromised as a result of myelosuppressive chemotherapy, organ transplantation, or "traditional" immunosuppressive illnesses, such as Hodgkin's disease.

The goal of this statement is to provide a framework for the *evaluation and therapy* of the patient with community-acquired pneumonia. The most common pathogens have been defined from published studies, and the determination of which diagnostic tests should be obtained routinely has been made on the basis of published data. While organism-directed antimicrobial therapy would be ideal because of reduced costs, reduction in adverse drug reactions, and antibiotic selection pressure, the limitations of our current diagnostic methods force us to rely on empiric antibiotic therapy in most patients with CAP. The approach to such therapy must be based on an assessment of the likelihood that a given pathogen is causing disease in a given patient, a determination guided by information from the literature. The major variables that influence the spectrum of etiologic agents and the initial approach to therapy are the severity of illness at initial presentation, the presence of coexisting illness, and the presence of identified clinical risk factors for drug-resistant and unusual pathogens (Table 1). Patients with severe community-acquired pneumonia have a distinct epidemiology and a somewhat different distribution of etiologic pathogens than do patients with other forms of pneumonia (8, 9, 16, 19, 20, 23, 24, 47, 48). Once empiric therapy has been initiated, other decisions, such as the duration of therapy and the change from parenteral to oral therapy, become relevant. Finally, it is inevitable that empiric therapy will not be successful for all patients, and thus an approach is provided for use if the patient is not responding to the selected regimen.

Methodology Used to Prepare This Document

The development of these guidelines was by a committee composed of pulmonary, critical care, infectious disease, and general internal medicine specialists, in an effort to incorporate a variety of perspectives and to create a statement that was acceptable to a wide range of physicians. The committee originally met as a group, with each individual being assigned a topic for review and presentation to the entire group, during a two-day meeting. Each topic in the guideline was reviewed by more than one committee member, and following presentation of information, the committee discussed the data and formulated its recommendations. Each section of the statement was then prepared by committee members, and a draft document incorporating all sections was written. This document was circulated to the committee for review and modification and then the committee met again in May of 2000 to deliberate on suggested changes. The manuscript was then revised and circulated to the committee for final comment. This final statement represents the results of this process and the opinions of the majority of the committee. For any topic in which there was disagreement, the majority position was adopted.

We used an evidence-based approach for making final recommendations, after review of all available and relevant peer-reviewed studies (collected by literature search and selected by the experts reviewing each topic), published until December 2000. Much of the literature on the etiology, epidemiology, and diagnostic approach to respiratory infections is observational, and only a few therapy trials have been conducted in a prospective randomized fashion. Therefore, in grading the evidence supporting our recommendations, we used the following scale, similar to the approach used in the recently updated Canadian CAP statement (46): Level I evidence comes from well-conducted randomized controlled trials; Level II evidence comes from well-designed, controlled trials without

TABLE 1. MODIFYING FACTORS THAT INCREASE THE RISK OF INFECTION WITH SPECIFIC PATHOGENS

Penicillin-resistant and drug-resistant pneumococci
Age > 65 yr
β-Lactam therapy within the past 3 mo
Alcoholism
Immune-suppressive illness (including therapy with corticosteroids)
Multiple medical comorbidities
Exposure to a child in a day care center
Enteric gram-negatives
Residence in a nursing home
Underlying cardiopulmonary disease
Multiple medical comorbidities
Recent antibiotic therapy
Pseudomonas aeruginosa
Structural lung disease (bronchiectasis)
Corticosteroid therapy (> 10 mg of prednisone per day)
Broad-spectrum antibiotic therapy for > 7 d in the past month
Malnutrition

randomization (including cohort, patient series, and case control studies); Level III evidence comes from case studies and expert opinion. Level II studies included any large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of new therapies that were not collected in a randomized fashion. In some instances therapy recommendations come from antibiotic susceptibility data, without clinical observations, and these constitute Level III recommendations.

While numerous studies detailing the incidence and etiology of pneumonia have been published, all have limitations. The approach used in this statement is based on an evaluation of studies that were long enough to avoid seasonal bias and recent enough to include newly recognized pathogens. Therefore, we reviewed the available literature, emphasizing data from prospective studies of one or more years' duration, reported in the past 15 years, involving adults in North America and elsewhere (3–32, 37, 38, 47). We focused on studies that included an extensive diagnostic approach to define the etiologic pathogen, and which did not rely on sputum Gram's stain and culture alone for this determination. Most involved hospitalized patients, but a wide spectrum of patients was included, ranging from outpatients to those admitted to an intensive care unit. In some of the studies, patients were receiving antimicrobials at the time of initial diagnostic evaluation, and the committee considered information from such studies of uncertain reliability.

ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA

Types of Data Reviewed

While a rapid diagnosis is optimal in the management of community-acquired pneumonia, the responsible pathogen is not defined in as many as 50% of patients, even when extensive diagnostic testing is performed (3–5, 13–15). No single test is presently available that can identify all potential pathogens, and each diagnostic test has limitations. For example, sputum Gram's stain and culture may be discordant for the presence of *Streptococcus pneumoniae*, and these tests are also not able to detect frequently encountered pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp., and respiratory viruses (49, 50). In addition, several studies have reported that some patients with CAP can have mixed infection involving both bacterial and "atypical" pathogens. This type of mixed infection may require therapy of all the identified pathogens, but cannot be diagnosed initially with readily available clinical specimens (13, 15, 17). In addition, mixed infection can involve more than one bacterial species, or can involve both a bacterial pathogen and a viral organism (13, 17, 28).

The role of "atypical" pathogens is controversial because the frequency of these organisms is largely dependent on the diagnostic tests and criteria used, and it is uncertain whether these organisms infect along with a bacterial pathogen, or if they cause an initial infection that then predisposes to secondary bacterial infection (13, 17, 28). The very term "atypical" pathogen is potentially misleading since the clinical syndrome caused by these organisms is not distinctive (*see below*), but in this statement the term "atypical" is used to refer to a group of organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp.), rather than to a clinical picture. The data supporting the presence of atypical pathogen coinfection (which has varied in frequency from as low as 3% to as high as 40%) have generally been derived by serologic testing, documenting fourfold rises in titers to *M. pneumoniae*, *C. pneumoniae*, or Legionella spp., and some of these diagnoses have even been made with single high acute titers (14, 17). Since many of these diagnoses have not involved testing for the surface antigens of these pathogens, or cultures of respiratory secretions, the clinical significance of the serologic data remains uncertain.

In defining the bacteriology of CAP, we examined the likely etiologic pathogens for each patient category, adding new information about the emerging resistance of common CAP pathogens such as pneumococcus, *H. influenzae*, and *M. catarrhalis* (33–39). In addition, there is now an increased awareness of the importance of newly recognized pathogens (such as hantavirus) and of "atypical" pathogens. In most studies, a large number of patients have no defined etiology. This is likely a reflection of a number of factors, including prior treatment with antibiotics, the presence of unusual pathogens that go unrecognized (fungi, *Coxiella burnetii*), the presence of viral infection, the presence of a noninfectious mimic of CAP, and the presence of pathogens that are currently not identified or recognized.

Organisms Causing CAP in Outpatients

Relatively few studies have been conducted in ambulatory patients with CAP and in this group an unknown diagnosis is present in 40–50% of all patients (11, 12, 30, 31, 51). When a pathogen has been identified, the nature of the organisms has reflected the population studied and the types of diagnostic tests performed. With use of sputum culture, pneumococcus is the most commonly identified pathogen (9–20% of all episodes), while *M. pneumoniae* is the most common organism (accounting for 13–37% of all episodes) identified when serologic testing is performed (11, 12, 51). *Chlamydia pneumoniae* has been reported in up to 17% of outpatients with CAP (51). In the outpatient setting, *Legionella* spp. have also been seen, with rates varying from 0.7 to 13% of all patients (30). The incidence of viral infection is variable, but in one series was identified in 36% of patients (30). The incidence of gram-negative infection in ambulatory patients is difficult to define from currently available studies, but the complexity of the population that is currently treated out of the hospital is increasing, and many of these patients have well-identified risk factors for colonization of the respiratory tract by gram-negative bacilli, a common predisposing factor to pneumonia with these pathogens (52).

Organisms Causing CAP in Non-ICU-Hospitalized Patients

On the basis of a review of 15 published studies from North America, over 3 decades in primarily hospitalized patients, Bartlett and Mundy (22) concluded that *S. pneumoniae* was the most commonly identified pathogen (20–60% of all episodes), followed by *H. influenzae* (3–10% of all episodes), and then by *Staphylococcus aureus*, enteric gram-negatives, *Legionella*, *M. pneumoniae*, *C. pneumoniae*, and viruses (up to 10% of episodes for each of these latter agents). In addition, some patients (3–6%) have pneumonia due to aspiration. In all studies, an etiologic agent was not found in 20–70% of patients (4, 5, 8, 13, 14, 18, 21). For many years, patients with an unknown diagnosis were assumed to have the same distribution of pathogens as those with an established diagnosis, since the outcomes in both groups were similar, but one study of hospitalized patients suggested that many patients without a known diagnosis actually have pneumococcal infection (53).

In several studies of hospitalized patients with CAP, there has been a high incidence of atypical pathogen infection, primarily *M. pneumoniae* and *C. pneumoniae* among those outside the ICU, while the incidence of *Legionella* infection has been low in patients who are not admitted to the ICU (8, 13, 14, 15, 16, 17). The incidence of infection with these "atypical" organisms has been as high as 40–60% of all admitted patients, often as part of a mixed infection, but the findings have not been corroborated by all investigators (13, 17, 54). This high

incidence was identified primarily by serologic testing that included single high acute titers as well as a 4-fold rise between acute and convalescent titers, but the serologic criteria and diagnostic tests used for these organisms are not standardized, and include the use of IgG and IgM titers. When atypical pathogens have been identified, they have not been confined to the population of young and healthy patients, but rather have been found in patients of all age groups (14). Even in series that do not identify a high incidence of atypical pathogens, they are often part of a mixed infection when they are identified (13, 54). The importance of mixed infection is also uncertain, with some investigators reporting that coinfection with bacterial and atypical pathogens leads to a more complicated course than monomicrobial infection, while others report no impact on the clinical course (28, 54). On the basis of these data, it is difficult to define the importance of these organisms and the need for specific therapy. However, several outcome studies show that both inpatients and outpatients have a less complicated clinical course if a macrolide is used as part of the therapy regimen, or if a quinolone is used alone (55–58).

Enteric gram-negative bacteria are not common in CAP, but may be present in up to 10% of non-ICU-hospitalized patients. They have been found most commonly in those who have underlying comorbid illness (particularly COPD) on previous oral antibiotic therapy, in those coming from nursing homes, and those with hematologic malignancy or immune suppression (the latter not being covered in this statement) (8, 15, 16, 18, 19). In one study, enteric gram-negatives were identified in 9% of patients, and in 11% of all pathogens, and the presence of any of the following comorbidities was associated with an increased risk of infection (odds ratio 4.4) with these organisms: cardiac illness, chronic lung disease, renal insufficiency, toxic liver disease, chronic neurologic illness, diabetes, and malignancy active within the last year (15). Although the incidence of *P. aeruginosa* infection is not high in most patients with CAP, this organism was found in 4% of all CAP patients with an established etiologic diagnosis (14, 15). There is still controversy about the true incidence of gram-negative infection in patients with CAP, since diagnostic testing that involves sputum culture cannot always distinguish between colonization by these organisms and true infection. The incidence of gram-negative infection is not as high in all admitted patients with CAP, but rises among those admitted to the ICU, as discussed below (8, 16, 20, 47).

Organisms Causing CAP in Hospitalized Patients Requiring ICU Admission

While gram-negative aerobic organisms have been identified with an increased frequency in patients with CAP requiring intensive care, the most common organisms in patients falling into this category are pneumococcus, *Legionella*, and *H. influenzae*, with some series reporting *S. aureus* as a common pathogen (8, 9, 16, 23). In addition, atypical pathogens such as *C. pneumoniae* and *M. pneumoniae* can lead to severe illness, and in at least one study, these organisms were more common than *Legionella* in causing severe CAP (16). Overall, up to 10% of admitted patients with CAP are brought to the ICU, and pneumococcus is present in up to one-third of all patients (8, 9, 16, 20). Among patients admitted to the ICU, organisms such as *P. aeruginosa* have been identified, particularly in individuals with underlying bronchiectasis (8, 16, 20, 47). In this population, the Enterobacteriaceae have been found in up to 22% of patients, and up to an additional 10–15% of ICU patients in some series have infection with *P. aeruginosa* (20, 23, 47). In all of these series, 50–60% of patients with severe CAP have an unknown etiology, and the failure to define a pathogen in these patients has not been associated with a different outcome than if a pathogen is identified (20, 24).

Drug-resistant Pneumococcus in CAP

The emergence of DRSP is an increasingly common problem in the United States and elsewhere, with more than 40% of all pneumococci falling into this category by current *in vitro* definitions of resistance (35, 59–60a). Controversy continues, however, about the clinical relevance of *in vitro* resistance in the absence of meningitis, and whether the problem, as currently defined, requires new therapeutic approaches or whether the presence of resistance influences the outcome of CAP (33, 34, 37, 38, 59, 60). The current definitions of resistance include "intermediate-level" resistance with penicillin MIC values of 0.12–1.0 μg/ml, while "high-level" resistance is defined as MIC values of ⩾ 2.0 μg/ml (60). When resistance to penicillin is present, there is often *in vitro* resistance to other agents, including cephalosporins, macrolides, doxycycline, and trimethoprim/sulfamethoxizole (35, 60a). In one survey, with isolates collected as recently as 1998, when high-level penicillin resistance was present, *in vitro* resistance to cefotaxime was 42%, to meropenem 52%, to erythromycin 61%, and to trimethoprim/sulfamethoxizole 92% (60a). The newer antipneumococcal fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, trovafloxacin, and sparfloxacin), the ketolides, and vancomycin are active agents for DRSP, and linezolid, a newly available oxazolidinone, is also active against DRSP. Although quinolone resistant pneumococci have been uncommon, one recent report found that 2.9% of pneumococcal isolates from adults were ciprofloxacin resistant and that 4.1% of isolates with high level penicillin resistance were also quinolone (ciprofloxacin) resistant (61). When ciprofloxacin resistance was present, *in vitro* resistance to the newer quinolones was also present.

The clinical relevance of DRSP has been debated, but in the absence of meningitis, clinical failure with high-dose β-lactam therapy is currently unlikely (60). Using currently defined levels of resistance, most investigators have found no difference in mortality for patients infected with resistant or sensitive organisms, after controlling for comorbid illness, although patients with resistant organisms may have a more prolonged hospital stay (33, 34). One study has shown that suppurative complications (such as empyema) are more common in patients with penicillin-nonsusceptible organisms than in patients with susceptible organisms, even though the majority of patients received apparently adequate therapy (62). In Spain, where the incidence of high-level DRSP is higher than in the United States, the presence of resistance has been reported to cause a rise in mortality, which was not statistically significant (38). In another study of a population with a high incidence of HIV infection, the presence of high-level penicillin resistance (as defined above) was associated with increased mortality, in spite of most patients receiving therapy that appeared to be appropriate (63). A Centers for Disease Control and Prevention (CDC, Atlanta, GA) study has shown that the breakpoint for clinically relevant resistance to penicillin is an MIC value of ⩾ 4.0 μg/ml (37). At these levels, resistance was associated with increased mortality in patients with invasive disease (primarily bacteremia), provided that patients dying in the first 4 d of therapy were excluded from the analysis (37). When these levels of resistance are suspected (or documented), alternative agents to penicillin should be used, and these are discussed below, although routine therapy with vancomycin is rarely needed (60).

Not all patients in areas with high geographic rates of DRSP are likely to be infected with these organisms, and even in areas with high rates of resistance, organisms isolated from sputum and blood cultures are less commonly resistant than or-

ganisms isolated from the upper respiratory tract (64). Identified risk factors for DRSP include age > 65 years (odds ratio [OR], 3.8), alcoholism (OR, 5.2), noninvasive disease (suggesting possibly reduced virulence of resistant organisms) (OR, 4.5), β-lactam therapy within 3 mo (OR, 2.8), multiple medical comorbidities, exposure to children in a day care center, and immunosuppressive illness (38, 59, 65, 66). In one study, the effect of age was less clear, with individuals ⩾ age 65 yr having an odds ratio of 1.2 (95% confidence interval [CI], 1.0–1.5) corresponding to an incidence of DRSP of 24%, compared with an incidence of 19% in those aged 18–64 yr (60a).

PATIENT STRATIFICATION

Features Used to Define Patient Subsets

We divided patients into four groups on the basis of place of therapy (outpatient, hospital ward, or intensive care unit); the presence of coexisting cardiopulmonary disease (chronic obstructive pulmonary disease, congestive heart failure); and the presence of "modifying factors," which included the presence of risk factors for drug-resistant pneumococcus, the presence of risk factors for gram-negative infection (including nursing home residence), and the presence of risk factors for *Pseudomonas aeruginosa* (specifically in patients requiring ICU admission) (Table 1) (15, 19, 27). The history of cigarette smoking was not used to classify patients, since all of the recommended therapy regimens account for *H. influenzae*, the organism that is more likely to occur in smokers than in nonsmokers. In this approach to stratification, the place of therapy is a reflection of severity of illness, with the need for hospitalization and the need for ICU admission being defined by the criteria described in subsequent sections of this statement.

In the previous version of the ATS CAP guidelines, age was used as a major discriminating factor among patients to define bacterial etiology. This concept has not been corroborated by studies that have shown that age alone, in the absence of comorbid illness, has little impact on the bacterial etiology of CAP (18, 19, 67). As discussed above, the elderly patient can have infection by "atypical" pathogens, and enteric gram-negatives are common primarily in those with comorbid illness (particularly underlying COPD), recent antibiotic therapy, and in patients residing in nursing homes (8, 15). One pathogen whose presence may be impacted by age alone is drug-resistant *Streptococcus pneumoniae* (DRSP), with several studies showing that age > 65 is, by itself, a specific epidemiologic risk for CAP due to this organism, but is not an independent risk factor for other organisms (38, 59).

Risk factors for penicillin and drug-resistant pneumococcus were defined from the literature, and are summarized in Table 1. Risk factors for enteric gram-negatives include residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibiotic therapy (15, 18, 19, 52). The risk factors for *P. aeruginosa* include the presence of any of the following: structural lung disease such as bronchiectasis, corticosteroid therapy (> 10 mg of prednisone per day), broad-spectrum antibiotic therapy for > 7 d in the past month, malnutrition, and leukopenic immune suppression (the latter is not included in this statement) (8, 15, 16, 68).

Patient Subsets

Using these factors, the four patient groups were defined (Tables 2–5 and Figure 1) as the following:

I. Outpatients with no history of cardiopulmonary disease, and no modifying factors (Table 2)
II. Outpatients with cardiopulmonary disease (congestive heart failure or COPD) and/or other modifying factors (risk factors for DRSP or gram-negative bacteria) (Table 3)
III. Inpatients, not admitted to the ICU, who have the following (Table 4):
   a. Cardiopulmonary disease, and/or other modifying factors (including being from a nursing home)
   b. No cardiopulmonary disease, and no other modifying factors
IV. ICU-admitted patients who have the following (Table 5):
   a. No risks for *Pseudomonas aeruginosa*
   b. Risks for *Pseudomonas aeruginosa*

For each group, results from available studies were combined to identify the most common pathogens associated with pneumonia and an attempt was made to rank the incidence of pathogens broadly, but a precise numeric incidence or percentage was not included. Patients with nursing home-acquired pneumonias were included, with the realization that this population is unique, and that a knowledge of local (institution-specific) epidemics and antibiotic susceptibility patterns is necessary to choose optimal empiric therapy. However, the following pathogens are recognized more frequently in nursing home patients than in patients with the same coexisting illnesses who are residing in the community: methicillin-resistant *S. aureus* (MRSA), enteric gram-negative bacteria, *Mycobacterium tuberculosis*, and certain viral agents (i.e., adenovirus, respiratory syncytial virus [RSV], and influenza) (18, 69–71). A miscellaneous group is included in each of Tables 2–5 and represents organisms that were present in about 1% of patients in these studies, or pathogens that have been otherwise reported to occur in this setting.

Specific Pathogens for Each Patient Subset

The most common pathogens in Group I, that is, outpatients with no cardiopulmonary disease and no risks for DRSP or gram-negatives, include *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, and respiratory viruses (*Level II evidence*). Miscellaneous pathogens include *Legionella* sp. (usually a more severe illness), *M. tuberculosis*, and endemic fungi. Although *H. influenzae* can be seen in this group of patients, it is a particular concern if the patient has a history of cigarette smoking. This population has a mortality rate of < 1–5% (10,72).

For patients in Group II, the presence of cardiopulmonary disease (congestive heart failure or COPD), or the presence of

TABLE 2. GROUP I: OUTPATIENTS, NO CARDIOPULMONARY DISEASE, NO MODIFYING FACTORS*,†

Organisms	Therapy
Streptococcus pneumoniae	Advanced generation macrolide:
Mycoplasma pneumoniae	azithromycin or clarithromycin‡
Chlamydia pneumoniae (alone or	*or*
as mixed infection)	Doxycycline§
Hemophilus influenzae	
Respiratory viruses	
Miscellaneous	
Legionella spp.	
Mycobacterium tuberculosis	
Endemic fungi	

* Excludes patients at risk for HIV.
† In roughly 50–90% of the cases no etiology was identified.
‡ Erythromycin is not active against *H. influenzae* and the advanced generation macrolides azithromycin and clarithromycin are better tolerated.
§ Many isolates of *S. pneumoniae* are resistant to tetracycline, and it should be used only if the patient is allergic to or intolerant of macrolides.

TABLE 3. GROUP II: OUTPATIENT, WITH CARDIOPULMONARY DISEASE, AND/OR OTHER MODIFYING FACTORS[*,†]

Organisms	Therapy[‡]
Streptococcus pneumoniae (including DRSP)	β-Lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime)
Mycoplasma pneumoniae	
Chlamydia pneumoniae	
Mixed infection (bacteria plus atypical pathogen or virus)	
Hemophilus influenzae	
Enteric gram-negatives	
Respiratory viruses	*plus*
Miscellaneous	Macrolide or doxycycline[§]
Moraxella catarrhalis, Legionella spp., aspiration (anaerobes), *Mycobacterium tuberculosis*, endemic fungi	*or* Antipneumococcal fluoroquinolone (used alone)[‖]

* Excludes patients at risk for HIV.
† In roughly 50–90% of the cases no etiology was identified.
‡ In no particular order.
§ High-dose amoxicillin is 1 g every 8 h; if a macrolide is used, erythromycin does not provide coverage of *H. influenzae,* and thus when amoxicillin is used, the addition of doxycycline or of an advanced-generation macrolide is required to provide adequate coverage of *H. influenzae.*
‖ *See* text for agents.

TABLE 4. GROUP III: INPATIENTS, NOT IN ICU[*,†]

Organisms	Therapy[‡]
a. Cardiopulmonary Disease and/or Modifying Factors (Including Being from a Nursing Home)	
Streptococcus pneumoniae (Including DRSP)	Intravenous β-lactam[§] (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin)
Hemophilus influenzae	
Mycoplasma pneumoniae	
Chlamdia pneumoniae	
Mixed infection (bacteria plus atypical pathogen)	*plus*
Enteric gram-negatives	Intravenous or oral macrolide or doxycycline[‖]
Aspiration (anaerobes)	*or*
Viruses	Intravenous antipneumococcal fluoroquinolone alone
Legionella spp.	
Miscellaneous	
Mycobacterium tuberculosis, endemic fungi, *Pneumocystis carinii*	
b. No cardiopulmonary Disease, No Modifying Factors	
S. pneumoniae	Intravenous azithromycin alone
H. influenzae	If macrolide allergic or intolerant:
M. pneumoniae	Doxycycline
C. pneumoniae	and a β-lactam
Mixed infection (bacteria plus atypical pathogen)	*or*
Viruses	Monotherapy with an antipneumococcal fluoroquinolone
Legionella spp.	
Miscellaneous	
M. tuberculosis, endemic fungi, *P. carinii*	

* Excludes patients at risk for HIV.
† In roughly one-third to one-half of the cases no etiology was identified.
‡ In no particular order.
§ Antipseudomonal agents such as cefepime, piperacillin/tazobactam, imipenem, and meropenem are generally active against DRSP, but not recommended for routine use in this population that does not have risk factors for *P. aeruginosa.*
‖ Use of doxycycline or an advanced generation macrolide (azithromycin or clarithromycin) will provide adequate coverage if the selected β-lactam is susceptible to bacterial β-lactamases (*see text*).

risk factors for DRSP (including age > 65 yr) or gram-negatives (including being from a nursing home), changes the likely pathogens. Although pneumococcus remains the most likely pathogen, resistance to penicillin and other agents (macrolides, trimethoprim/sulfamethoxizole) is more likely, and this should be considered in antibiotic selection (below). In addition, if the patient is from a nursing home, then aerobic gram-negative infection is possible and can include the Enterobacteriaceae such as *Escherichia coli*, or *Klebsiella* spp., and even *P. aeruginosa* (if bronchiectasis is present) (*Level II evidence*). Also, in this population, aspiration with anaerobes should be considered in the presence of poor dentition and if the patient has a history of neurologic illness, impaired consciousness, or a swallowing disorder. Less common pathogens include *Moraxella catarrhalis*, *Legionella* sp., *Mycobacterium* sp., and endemic fungi. Mortality in this setting is also < 5%, but as many as 20% of patients initially treated as outpatients may require hospitalization (72).

When the patient is hospitalized, there are usually risks for DRSP and enteric gram-negatives, or underlying cardiopulmonary disease, and these factors influence the likely pathogens (Group IIIa). These patients are at risk for infection with pneumococcus, *H. influenzae*, atypical pathogens (alone or as a mixed infection), as well as enteric gram-negatives such as the Enterobacteriaceae, and also a polymicrobial bacterial flora including anaerobes associated with aspiration (if risk factors are present). All admitted patients are also at risk for *M. tuberculosis* and endemic fungi, but these are less commonly identified than the other organisms listed above. Tuberculosis is a particular concern in patients who have been born in foreign countries with high rates of endemic illness, in the alcoholic, and in the elderly who reside in nursing homes. Mortality rates reported for these patients ranged from 5 to 25%, and most of the deaths occurred within the first 7 d (3, 10). If, however, the admitted patient has no cardiopulmonary disease, and no risks for DRSP or gram-negatives (Group IIIb), then the most likely pathogens are *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, viruses, and possibly *Legionella* sp. (*Level II evidence*).

In some studies of admitted patients with CAP, the etiology may be polymicrobial. The incidence of "mixed" infection, usually a bacterial pathogen and an "atypical" pathogen, varies from < 10% to up to 40% (10, 12, 13, 17, 28). Atypical pathogens have been frequently identified in admitted patients of all age groups. The difference in relative incidence of "mixed" infections may relate to how aggressively investigators collected both acute and convalescent titers, and to the type of criteria used to define the presence of these pathogens (single-titer versus 4-fold rise in titers) (13, 17).

Severe community-acquired pneumonia (defined below) has been separated from cases of less severe pneumonia requiring hospitalization, because of the high mortality rate (up to 50%) and the need for immediate recognition of patients with this severity of illness (8–10, 16, 10, 24, 47, 48). Although severe pneumonia was defined differently by the various investigators, a practical approach defines all patients admitted to the ICU because of respiratory infection as having severe illness (*see below*) (48). The pathogens most frequently identified among patients with severe pneumonia (Group IVa) include *S. pneumoniae*, *Legionella* sp., *H. influenzae*, enteric gram-negative bacilli, *S. aureus*, *M. pneumoniae*, respiratory tract viruses, and a group of miscellaneous pathogens (*C. pneumoniae*, *M. tuberculosis*, and endemic fungi) (8, 9, 16, 19, 20, 23, 47). In one study, the incidence of *Legionella* sp. in patients with severe CAP decreased over time, in one hospital, but was replaced by other atypical pathogens, such as *C. pneumoniae* and *M. pneumoniae* (16). There has been some debate about whether *P. aeruginosa* can lead to severe CAP, and although this organism has been reported in some studies (in 1.5–5% of such patients), the committee felt that this pathogen should be considered only when specific risk factors are present (Group IVb) (8, 16, 20, 47) (*Level III evidence*). These risks include chronic or prolonged (> 7 d within the past month) broad-

TABLE 5. GROUP IV: ICU-ADMITTED PATIENTS*,†

Organisms	Therapy‖,‡
a. No Risks for *Pseudomonas aeruginosa*	
Streptococcus pneumoniae (including DRSP) *Legionella* spp. *Hemophilus influenzae* Enteric gram-negative bacilli *Staphylococcus aureus* *Mycoplasma pneumoniae* Respiratory viruses Miscellaneous *Chlamydia pneumoniae*, *Mycobacterium tuberculosis*, endemic fungi	Intravenous β-lactam (cefotaxime, ceftriaxone)§ *plus either* Intravenous macrolide (azithromycin) *or* Intravenous fluoroquinolone
b. Risks for *Pseudomonas aeruginosa*‖	
All of the above pathogens plus *P. aeruginosa*	Selected intrevenous antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam)# *plus* intravenous antipseudomonal quinolone (ciprofloxacin) *or* Selected intravenous antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam)# *plus* intravenous aminoglycoside *plus either* intravenous macrolide (azithromycin) *or* intravenous nonpseudomonal fluoroquinolone

* Excludes patients at risk for HIV.
† In roughly one-third to one-half of the cases no etiology was identified.
‡ In no particular order.
§ Antipseudomonal agents such as cefepime, piperacillin/tazobactam, imipenem, and meropenem are generally active against DRSP and other likely pathogens in this population, but not recommended for routine use unless the patient has risk factors for *P. aeruginosa.*
‖ Combination therapy required.
If β-lactam allergic, replace the listed β-lactam with aztreonam and combine with an aminoglycoside and an antipneumococcal fluoroquinolone as listed.

spectrum antibiotic therapy, or the presence of bronchiectasis, malnutrition, or diseases and therapies associated with neutrophil dysfunction (such as > 10 mg of prednisone per day). Undiagnosed HIV infection has been identified as a risk factor for CAP due to *P. aeruginosa* (73). The frequency of *S. aureus* as a severe CAP pathogen is also variable, being present in anywhere from 1 to 22% of all patients. Risks for infection with this organism include recent influenza infection, diabetes, and renal failure (74).

DIAGNOSTIC STUDIES OF PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

The diagnosis of pneumonia should be considered in any patient who has newly acquired respiratory symptoms (cough, sputum production, and/or dyspnea), especially if accompanied by fever and auscultatory findings of abnormal breath sounds and crackles. In a patient with advanced age or an inadequate immune response, pneumonia may present with nonrespiratory symptoms such as confusion, failure to thrive, worsening of an underlying chronic illness, or falling down (21, 71). In these patients, fever may be absent, but tachypnea is usually present, along with an abnormal physical examination of the chest (75). In the initial evaluation of the patient with CAP, the history may on occasion help to identify patients at risk for infection with specific organisms, as outlined in Table 6.

Standard posteroanterior (PA) and lateral chest radiographs are valuable in patients whose symptoms and physical examination suggest the possibility of pneumonia, and every effort should be made to obtain this information. The radiograph can be useful in differentiating pneumonia from other conditions that may mimic it. In addition, the radiographic findings may suggest specific etiologies or conditions which as lung abscess, or tuberculosis. The radiograph can also identify coexisting conditions such as bronchial obstruction or pleural effusion. In some patients, the history and physical examination suggest the presence of pneumonia, but the radiograph is negative. One study has shown that some of these radiographically negative patients do have lung infiltrates if a high-resolution computed tomography (CT) scan of the chest is done (76). However, the clinical relevance of these findings is uncertain, since most studies of CAP have required the presence of a lung infiltrate on a routine chest radiograph to define the presence of pneumonia. Radiography is also useful for evaluating severity of illness by identifying multilobar involvement (below). However, in certain outpatient settings, depending on the time of day and the availability of a radiology facility, it may be difficult to obtain a chest radiograph.

Once the diagnosis of CAP is established, an effort should be made to identify a specific etiologic diagnosis in a timely manner, with focused and appropriate diagnostic testing. However, even with extensive diagnostic testing, most investigators cannot identify a specific etiology for community-acquired pneumonia in up to half, or more, of all patients. If an exact etiology is identified, then therapy can be focused and cost-effective, but this goal needs to be tempered by two findings. First, if diagnostic testing leads to delays in the initiation of appropriate therapy, it may have an adverse outcome. One large Medicare study showed that 30-d CAP mortality was increased when administration of the first dose of antibiotic

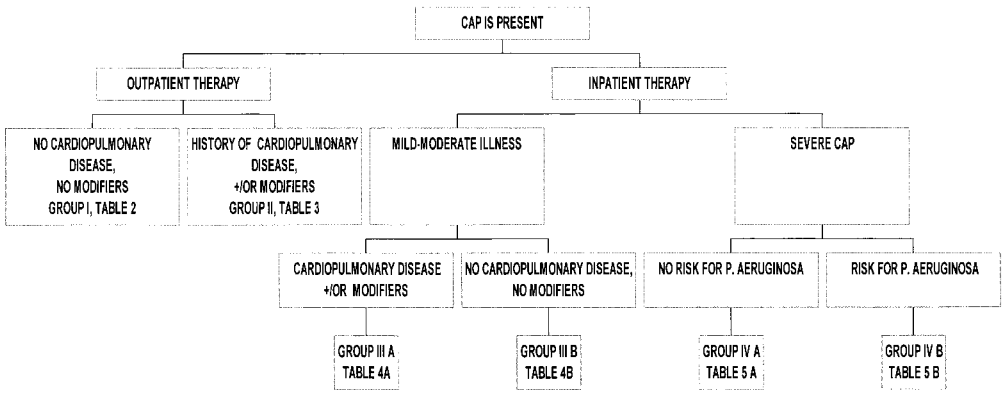

Figure 1.

TABLE 6. EPIDEMIOLOGIC CONDITIONS RELATED TO SPECIFIC PATHOGENS IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Condition	Commonly Encountered Pathogens
Alcoholism	*Streptococcus pneumoniae* (including DRSP), anaerobes, gram-negative bacilli, tuberculosis
COPD/smoker	*S. pneumoniae, Hemophilus influenzae, Moraxella catarrhalis, Legionella*
Nursing home residency	*S. pneumoniae,* gram-negative bacilli, *H. influenzae, Staphylococcus aureus,* anaerobes, *Chlamydia pneumoniae,* tuberculosis
Poor dental hygiene	Anaerobes
Epidemic Legionnaire's disease	*Legionella* species
Exposure to bats	Histoplasma capsulatum
Exposure to birds	*Chlamydia psittaci, Cryptococcus neoformans, H. capsulatum*
Exposure to rabbits	*Francisella tularensis*
Travel to southwest United States	Coccidioidomycosis
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Influenza active in community	Influenza, *S. pneumoniae, S. aureus, H. influenzae*
Suspected large-volume aspiration	Anaerobes, chemical pneumonitis, or obstruction
Structural disease of lung (bronchiectasis, cystic fibrosis, etc.)	*P. aeruginosa, Pseudomonas cepacia,* or *S. aureus*
Injection drug use	*S. aureus,* anaerobes, tuberculosis, *Pneumocystis carinii*
Endobronchial obstruction	Anaerobes
Recent antibiotic therapy	Drug-resistant pneumococci, *P. aeruginosa*

therapy was delayed more than 8 h from the time of arrival to the hospital (77). Second, since the possibility of coinfection is a consideration, with a bacteria and an atypical pathogen (which may take days or weeks to identify), the value of focused therapy, directed at a rapidly identified bacterial etiology, is uncertain. In fact, in large population studies, treatment that accounted for atypical pathogen coinfection led to a better outcome than treatment that did not account for this possibility (55–57) (*Level II evidence*).

One of the most controversial recommendations in the 1993 ATS guidelines for CAP was that a sputum Gram's stain and culture not be performed routinely in all admitted patients (44). Although its value is debated, some experts, including the IDSA consensus group, believe that a properly collected and examined Gram's stain of expectorated sputum is helpful for focusing initial empiric therapy in CAP (45). A lower respiratory tract sample that is not heavily contaminated by oral secretions will typically have fewer than 10 squamous epithelial cells, and $>$ 25 neutrophils per low-power field (45). Studies of the sputum Gram's stain have shown limitations, which include the following: not all patients can provide an adequate sample (either because of an inability to produce a sample, or because the sample is of poor quality), interpretation is observer dependent, atypical pathogens (which are common either singly or as coinfecting agents, as discussed above) cannot be seen, the definition of "positive" varies from study to study, and a positive result for pneumococcus is poorly predictive of the ability to recover that organism from a sputum or blood culture (49, 50). In addition, there are no studies correlating data from Gram's stain of expectorated sputum with cultures of alveolar material in large numbers of patients with community-acquired pneumonia. However, direct staining of sputum (non-Gram stain methods) may be diagnostic for some pulmonary infections including those due to *Mycobacterium* sp., endemic fungi, *Legionella* sp. (direct fluorescent antibody staining is required), and *Pneumocytis carinii.*

If a sputum Gram's stain is used to determine initial therapy, the clinician must decide whether liberal criteria are being used to increase the sensitivity of the test (with a corresponding drop in specificity), or whether more stringent criteria are being used to increase the specificity of the test (with a corresponding drop in sensitivity) (49). The debate about the value of Gram's stain may be less relevant with the advent of the Clinical Laboratory Improvement Act, which has limited the use of this test to laboratory personnel who often interpret the results without knowledge of the clinical scenario and suspected pathogens.

Routine bacterial cultures of sputum often demonstrate pathogenic organisms, but sensitivity and specificity are poor, and findings should be correlated with the predominant organism identified on Gram's stain (50). However, recovery from cultures of organisms that are not usually part of the normal respiratory flora may be meaningful. Specialized cultures for *Mycobacterium* sp., *Legionella* sp., and endemic fungi may be valuable in the appropriate clinical circumstance. When drug-resistant pneumococci, other resistant pathogens, or organisms not covered by the usual empiric therapy options (such as *S. aureus*) are anticipated (particularly if the patient has risk factors, or is receiving antibiotics at the time of admission) sputum culture and sensitivity results may be useful. Viral cultures are not useful in the initial evaluation of patients with community-acquired pneumonia and should not be routinely performed (3). However, in the appropriate season, testing of respiratory secretions for influenza antigens, using rapid detection methods, may be helpful in guiding decisions about the use of new antiviral agents.

Recommended Testing

For the patient with CAP initially managed out of the hospital, diagnostic testing should include a chest radiograph and may include a sputum Gram's stain and culture, if drug-resistant bacteria, or an organism not covered by the usual empiric therapy options, are suspected (*Level II evidence*). In addition, it is necessary to assess severity of illness, relying on radiographic findings (multilobar pneumonia, pleural effusion), and physical findings (respiratory rate, systolic and diastolic blood pressure, signs of dehydration, and mental status) (78–80). If the patient has underlying chronic heart or lung disease, then assessment of oxygenation by pulse oximetry may help define the need for hospitalization and supplemental oxygen. Routine laboratory tests (complete blood counts, serum electrolytes, hepatic enzymes, and tests of renal function) are of little value in determining the etiology of pneumonia, but may have prognostic significance and influence the decision to hospitalize. They should be considered in patients who may need hospitalization, and in patients $>$ age 65 yr or with coexisting illness (*Level II evidence*).

For the patient who is admitted, diagnostic testing should be performed rapidly, avoiding delays in the administration of initial empiric therapy, for the reasons stated above. In addition to a chest radiograph, an admitted patient should have a complete blood count and differential, and routine blood chemistry testing (including glucose, serum sodium, liver and renal function tests, and electrolytes) (*Level III evidence*). All admitted patients should have oxygen saturation assessed by oximetry. Arterial blood gas should be obtained in any patient with severe illness, or in any patient with chronic lung disease, to assess both the level oxygenation and the degree of carbon dioxide retention. Sputum cultures are recommended if a drug-resistant pathogen, or an organism not covered by usual em-

piric therapy, is suspected. If a sputum culture is obtained, efforts should be made to collect it prior to antibiotic administration. Any culture result should be correlated with the predominant organism identified on Gram's stain of an appropriate specimen, which should be performed in conjuction with a sputum culture (*Level III evidence*). Otherwise, in the absence of a culture, a sputum Gram's stain is optional. However, it is the consensus of the majority of the CAP statement committee that if a sputum Gram's stain is used to guide initial therapy, it should be with highly sensitive criteria (any gram-positive diplococci, rather than a predominance of such organisms), with the primary purpose being to visualize a bacterial morphology of an organism that was not anticipated, so that appropriate drugs can be added to the initial antibiotic regimen (e.g., *S. aureus*, or enteric gram-negatives) (*Level III evidence*). This conclusion differs from that of the IDSA consensus group, which recommended using Gram's stain to narrow initial empiric therapy in patients with certain organism-specific findings (45). Two sets of blood cultures should be drawn before initiation of antibiotic therapy, and may help to identify the presence of bacteremia and of a resistant pathogen, with the overall yield being approximately 11%, and with *S. pneumoniae* being the most common pathogen identified by this method (46). Any significant pleural effusion (> 10-mm thickness on lateral decubitus film) or any loculated pleural effusion should be sampled, preferably prior to the initiation of antibiotic therapy, to rule out the possibility of empyema or complicated parapneumonic effusion; however, there are no data showing an outcomes benefit to delaying antibiotic therapy for the purpose of performing a thoracentesis. Pleural fluid examination should include white blood cell count and differential; measurement of protein, glucose, lactate dehydrogenase (LDH) and pH; Gram's stain and acid-fast stain; as well as culture for bacteria, fungi, and mycobacteria.

Serologic testing and cold agglutinin measurements are not useful in the initial evaluation of patients with community-acquired pneumonia and should not be routinely performed (*Level II evidence*). However, acute and convalescent serologic testing may occasionally be useful for a retrospective confirmation of a suspected diagnosis and may be useful in epidemiologic studies. When *Legionella* is suspected (patients with severe CAP), measurement of urinary antigen is valuable, being positive in the majority of patients with acute *Legionella pneumophila* serogroup 1 infection, but the test can remain positive for many months after the acute infection (81, 82). Serial complement-fixing antibody titers may be useful in monitoring patients with extensive coccidioidomycosis, and sputum cultures for endemic fungi should be collected in at-risk patients with the proper epidemiologic history. Although patients known to be immune suppressed are excluded from this statement, HIV testing should be done (after informed consent) in any CAP patient with risk factors and should be considered in any patient aged 15–54 yr who is admitted for CAP (83). Specialized tests that measure microbial antigens by monoclonal antibodies, DNA probes, and polymerase chain reaction amplification are being developed, but have not been shown to be valuable for routine use in patients with CAP.

A number of invasive diagnostic techniques to obtain lower airway specimens, uncontaminated by oropharyngeal flora, have been described (45, 84, 85). These include transtracheal aspiration, bronchoscopy with a protected brush catheter, bronchoalveolar lavage with or without balloon protection, and direct percutaneous fine needle aspiration of the lung. These procedures are not indicated in most patients with community-acquired pneumonia (*Level III evidence*). It may be desirable to have an early accurate diagnosis in occasional patients who are severely ill, although retrospective data have shown that with severe illness, outcome is not improved by establishing a specific etiologic diagnosis (20, 24). In such patients, bronchoscopy with a protected brush catheter or bronchoalveolar lavage has a reasonable sensitivity and specificity when performed correctly. These procedures carry less risk and are usually more acceptable to patients and physicians than transtracheal aspiration and direct needle aspiration of the lung, although some physicians have special expertise in using ultrathin needles for direct lung aspiration.

Although the committee recommended limited initial diagnostic testing, it is necessary to do more extensive testing in patients whose illness is not resolving in spite of apparently appropriate empiric therapy (*see below*). As discussed above, this statement is not directed at patients known to be immune suppressed. Such patients require a different and more extensive diagnostic approach that reflects the wide range of potential pathogens in this population.

THE ROLE OF CLINICAL SIGNS AND SYMPTOMS IN PREDICTING THE MICROBIAL ETIOLOGY OF CAP

The clinical features of CAP (symptoms, signs and radiographic findings) cannot be reliably used to establish the etiologic diagnosis of pneumonia with adequate sensitivity and specificity (*Level II evidence*). Although, in some circumstances, clinicians can confidently use clinical features to establish a specific etiologic diagnosis, in the majority of cases this is not possible. This relates not only to variations in virulence factors of particular pathogens, but also to the presence of coexisting illnesses, resulting in an overlap of clinical symptoms among various etiologic pathogens.

Typical versus Atypical Pneumonia Syndromes

Originally, the classification of pneumonia into "atypical" and "typical" forms arose from the observation that the presentation and natural history of some patients with pneumonia were different compared with those of patients with pneumococcal infection (86, 87). Some pathogens, such as *H. influenzae*, *S. aureus*, and gram-negative enteric bacteria, caused clinical syndromes identical to those produced by *S. pneumoniae* (88). However, other pathogens caused an "atypical" pneumonia syndrome that was initially attributed to *M. pneumoniae* (87), but other bacterial and viral agents have been identified that can produce a subacute illness indistinguishable from that caused by *M. pneumoniae* (89, 90). Some of these agents, however, like *Legionella* species and influenza, can cause a wide spectrum of illness, ranging from a fulminant life-threatening pneumonia to a more subacute presentation (90). Thus the term "atypical" pneumonia represents a clinical syndrome that includes diverse entities, and has limited clinical value.

The attribution of specific clinical features to an etiologic agent is a common clinical practice, particularly for patients suspected of having pneumonia caused by *Legionella* species. However, data have cast doubt on the specificity of these observations (4, 15, 18), leading to the conclusion that the diagnosis of *Legionella* sp. infection could not be made on clinical grounds alone. Other comparative studies involving both pediatric and adult populations, have concluded that an etiologic diagnosis could not be established by clinical criteria alone (91–93). In addition, no roentgenographic pattern is sufficiently distinctive to allow classification of individual cases (94, 95).

Advanced age and coexisting illness are important factors that affect the clinical presentation of pneumonia. Individuals over the age of 65 yr are particularly at risk for mortality from bacteremic pneumococcal disease, and among the elderly, the

expression of common clinical features of pneumonia is often atypical, obscured, or even absent (71, 96, 97). Thus, because host factors are often just as important as the identity of the etiologic pathogen in defining the presenting signs and symptoms of pneumonia, the committee felt that it is not possible to reliably use clinical features, including history, physical examination, and routine laboratory and roentgenographic evaluation, to make a specific etiologic diagnosis of community-acquired pneumonia (*Level II evidence*).

THE DECISION TO HOSPITALIZE PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

The initial site-of-care decision is perhaps the single most important clinical decision made by physicians during the entire course of illness for patients with community-acquired pneumonia (CAP). It has a direct bearing on the intensity of laboratory testing, microbiologic evaluation, antibiotic therapy, and costs of treating this illness. The estimated average cost of inpatient care for CAP is U.S. $7,500, compared with U.S. $150–$350 for outpatient care (2, 98).

Defining Risk Factors for a Complicated Course of CAP to Determine the Need for Admission

Studies have identified a series of risk factors that increase either the likelihood of death or the risk of a complicated course for community-acquired pneumonia (10, 72). When *multiple* risk factors coexist, the committee believed that hospitalization should be strongly *considered* (*Level II evidence*). The decision to hospitalize is not necessarily a commitment to long-term inpatient care but, rather, a decision that certain patients should be observed closely until it is clear that therapy can be safely continued out of the hospital. The admission decision may also be influenced by the availability of outpatient support services (home nursing, home intravenous therapy), and alternative sites for care (subacute care facilities). Since criteria for admission have not been uniformly applied by clinicians, studies have reported wide geographic variation in hospital admission rates for CAP (99). In addition, in some studies physicians have overestimated the risk of death for patients with CAP, leading to unnecessary admissions, while in other studies they have failed to recognize patients as being severely ill at the time of initial evaluation (72, 80).

Risk factors associated with an increased risk of death or a complicated course have been identified, and in one study, admitted patients had a mean of five risk factors present (57). All of these studies were observational, and the risk factors for an adverse outcome were defined only in hospitalized patients who had received antibiotics and supportive care for their illness, and the risk factors have not been studied in large numbers of outpatients. These factors include a number of features listed below, and those with an asterisk (*) are factors that have been identified to predict mortality in the PORT prediction rule model (72):

1. Age over 65 yr
2. Presence of coexisting illnesses such as chronic obstructive lung disease, bronchiectasis, malignancy (*), diabetes mellitus, chronic renal failure (*), congestive heart failure (*), chronic liver disease (*), chronic alcohol abuse, malnutrition, cerebrovascular disease (*), and postsplenectomy. A history of hospitalization within the past year is also a risk factor
3. Certain physical findings also predict either mortality, increased morbidity, or a complicated course (10,79,80,100). These physical findings include a respiratory rate $\geq$ 30 breaths/min (*); diastolic blood pressure $\leq$ 60 mm Hg or systolic blood pressure $<$ 90 mm Hg (*); pulse $\geq$ 125/min (*); fever $<$ 35 or $\geq$ 40° C (*); confusion or decreased level of consciousness (*); and evidence of extrapulmonary sites of infection
4. Laboratory findings also predict increased morbidity or mortality:
   a. White blood cell count $< 4 \times 10^9$/L or $> 30 \times 10^9$/L, or an absolute neutrophil count below 1×10^9/L
   b. $Pa_{O_2} <$ 60 mm Hg (*) or Pa_{CO_2} of $>$ 50 mm Hg while breathing room air
   c. Evidence of abnormal renal function, as manifested by serum creatinine of $>$ 1.2 mg/dl or a BUN of $>$ 20 mg/dl ($>$ 7 mM) (79)
   d. Presence of certain unfavorable chest radiograph findings, for example, more than one lobe involvement, presence of a cavity, rapid radiographic spreading (which usually cannot be determined at the time of admission) (8); and the presence of a pleural effusion (*) (78)
   e. Hematocrit of $<$ 30% (*) or hemoglobin $<$ 9 mg/dl
   f. Evidence of sepsis or organ dysfunction as manifested by a metabolic acidosis, or coagulopathy
   g. Arterial pH $<$ 7.35 (*)

Social considerations also enter into the decision to hospitalize. The absence of a responsible caregiver in a stable home situation is a strong indication for hospitalization, at least for observation purposes. Since community-acquired pneumonia remains a significant cause of morbidity and mortality, the committee felt that the admission decision remains an "art of medicine" decision. Thus, when the overall appearance of the patient seems unfavorable, even if the above-mentioned criteria are not fully met, consideration should be given to placing the patient in the hospital on observation status for 24 to 48 h, or until such time as these concerns are resolved (*Level III evidence*). In studies where objective criteria for admission have been applied, at least 30% of "low-risk" patients have been admitted, reflecting the need to hospitalize some patients who do not meet objective standards (101) (*Level I evidence*).

Using Prognostic Scoring Systems to Define the Admission Decision

The above-described approach is not quantitative, and in the past 10 years, multiple studies have used multivariate analysis to develop prediction rules for outcome in CAP that could be used to help with the initial site of care decision (72, 102–104). However, none of these rules was specifically designed to define need for hospitalization. One approach, developed by the British Thoracic Society (BTS) Research Committee, was aimed at identifying high-risk patients who not only usually require admission, but who also often require ICU care (79, 80). The other approach, developed by the Pneumonia Patient Outcomes Research Team (PORT), separated patients into high and low risk of death, and that categorization has been extrapolated into defining the need for admission (72). These two prediction rules, developed and validated in different ways, are complementary. The BTS rule is focused on identifying high-risk patients so that their severity of illness is not underestimated, while the Pneumonia PORT approach is focused on recognizing some patients as low risk, so that their severity of illness is not overestimated.

The Pneumonia PORT prediction rule used a derivation cohort of 14,199 inpatients with CAP; it was independently validated in 38,039 inpatients with CAP and in 2,287 inpatients and outpatients prospectively enrolled in the Pneumonia PORT cohort study (72). One limitation in the derivation of this rule was that it included mostly patients seen in a hospital emer-

gency department, and included few outpatients who were evaluated in a physician's office and sent home. In applying this rule, patients were stratified into five severity classes, using a two-step process that evaluated a number of demographic factors, comorbid illnesses, physical findings, and laboratory and radiographic data. In the derivation and validation of this rule, mortality ranged from 0.1 to 0.4% in Class I, 0.6 to 0.7% in Class II, and 0.9 to 2.8% in Class III. Mortality was intermediate for Class IV (8.2 to 9.3%) and high for Class V (27.0 to 31.1%). Increasing risk class was also associated with subsequent hospitalization among individuals initially managed as outpatients and with need for ICU admission (72).

On the basis of these observations, the Pneumonia PORT investigators hypothesized that patients in risk Class I or II be considered for outpatient treatment. Patients in risk Class III were potential candidates for outpatient treatment or brief inpatient observation, while traditional inpatient care should be provided for patients in Classes IV and V. No attempt was made to use risk stratification for the purpose of defining the need for admission to the ICU. Using this approach, they estimated that the proportion of patients receiving traditional inpatient care could be reduced by 31%. Of the Pneumonia PORT inpatients who would have been recommended for outpatient care under this strategy, 1% died and 4.3% were admitted to an ICU (72). If the strategy were amended to include traditional inpatient care for any patient (including those in low risk groups) with arterial hypoxemia ($Po_2 < 60$ mm Hg or O_2 saturation $< 90\%$ on room air) at the time of presentation, then the reduction in inpatient care would have been slightly less dramatic, but the number of ICU admissions, for inpatients who were initially recommended for outpatient care, would have been reduced.

While the authors have extrapolated these data to define the need for hospitalization, the Pneumonia PORT prediction rule was actually derived to define mortality risk. In addition, it was never prospectively tested, during its development, for the purpose of defining the need for hospitalization. Prospective studies of the utility of the rule for deciding initial site of care of patients presenting to an emergency department (ED) have been published (101, 105). In one study, application of the Pneumonia PORT rule reduced the percentage of low-risk patients who were admitted (compared with a preceding control year) from 58 to 43%, but 9% of patients who were initially discharged according to the rule subsequently required admission (105). In another study conducted in 19 Canadian hospitals, 9 hospitals were randomized to use a critical pathway for pneumonia care that included calculation of the Pneumonia PORT severity index when patients arrived in the emergency department (101). Although the pathway recommended that patients in risk categories I–III be discharged, physician decision was allowed to supersede this guideline. In the hospitals that used the critical pathway, the number of low-risk patients admitted was significantly lower than in the hospitals that did not use the pathway. However, even with the use of the Pneumonia PORT rule, 31% of low-risk patients were admitted (compared with 49% in the control group). The patients in the critical pathway hospitals had the same outcome as those in the control hospitals. Since the pathway contained many interventions, the impact of any one factor (such as the Pneumonia PORT prediction rule) was not evaluated.

The BTS prediction rule was derived using 453 inpatients with CAP and was independently validated in 246 inpatients (79). The rule defines a patient as high risk for mortality if at least two of three features are present: respiratory rate ≥ 30/min, diastolic blood pressure ≤ 60 mm Hg, and BUN > 7.0 mM (> 19.1 mg/dl). Patients with two or more of these prognostic factors had a relative risk of death of 21.1 (19.4 versus 0.9%) and 9.1 (28.6 versus 3.1%) in the derivation and validation cohorts, respectively. A fourth factor, confusion, has been added to the rule and in one study, patients with any two of these four factors present had a 36-fold increase in mortality compared with those without these findings (80). In addition, in that study, when calculated on admission, the BTS rule identified as severely ill 19 patients who subsequently died, while clinicians identified only 12 of these 19 as being severely ill, based on their clinical assessment. These data suggest a value for the BTS rule to identify high-risk patients in a simple and reliable fashion (*Level II evidence*).

Recommendations for the Admission Decision

Prediction rules may oversimplify the way physicians interpret predictor variables, since each variable has a "threshold" for being a poor prognostic finding. Thus, in the Pneumonia PORT approach, a patient with a diastolic blood pressure of 56 mm Hg falls into the same stratification as a patient with a diastolic blood pressure of 30 mm Hg, even though the two patients have profoundly different severity of illness. In addition, the Pneumonia PORT rule assigns points in a way that heavily weights age, requiring much more severe physiologic abnormalities in young patients compared with older patients, in order to fall into a risk group requiring admission. Finally, prediction rules neglect the importance of patient preferences in clinical decision-making. This point is highlighted by the observations that the vast majority of low-risk patients with CAP do not have their preferences for site of care solicited, even though many have a strong preference for outpatient care (106).

The committee felt that mortality prediction rules should be used to support, but not replace, physician decision making. Patients may have rare conditions, such as severe neuromuscular disease or prior splenectomy, that are not included as factors in these prediction rules but that increase the likelihood of a poor prognosis. In addition, factors other than severity of illness must be considered, and patients designated as "low risk" may have important medical and psychosocial contraindications to outpatient care. Ability to maintain oral intake, history of substance abuse, cognitive impairment, and ability to carry out activities of daily living should be considered (*Level III evidence*). Thus, determination of the initial site of care remains an "art of medicine" decision that cannot be easily made by any of the existing prediction models.

DEFINITION OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA AND NEED FOR ADMISSION TO THE ICU

Severe community-acquired pneumonia is an entity described in the literature in reference to patients with CAP admitted to the ICU. The incidence, etiology, prognostic factors, and outcome of these patients have been defined, and differ from those in the overall population of patients with community-acquired pneumonia. Studies have shown that patients with severe community-acquired pneumonia have a distinct spectrum of etiologic agents (8, 9, 16) (*Level II evidence*).

Early recognition of patients with severe CAP will aid in the initiation of prompt therapy directed at the likely etiologic pathogens, a strategy associated with reduced mortality, if it leads to a clinical improvement within 72 h (20). Although there is no uniformly accepted definition of severe CAP, the original ATS guidelines identified nine criteria for severe illness, and the presence of any one was used to define severe CAP. Subsequently, several studies have shown that when only one of these criteria is used, as many as 65–68% of all admitted patients have "severe CAP," indicating that the original definition was overly sensitive, and not specific (48, 57).

In one more recent study, the nine criteria for severe CAP were divided into five "minor" criteria that could be present on admission and four "major" criteria that could be present on admission or later in the hospital stay (48). The minor criteria included respiratory rate $\geq$ 30/min, $Pa_{O_2}/FI_{O_2} < 250$, bilateral pneumonia or multilobar pneumonia, systolic BP $\leq$ 90 mm Hg, and diastolic BP $\leq$ 60 mm Hg. The major criteria included a need for mechanical ventilation, an increase in the size of infiltrates by $>$ 50% within 48 h, septic shock or the need for pressors for $>$ 4 h, and acute renal failure (urine output $<$ 80 ml in 4 h or serum creatinine $>$ 2 mg/dl in the absence of chronic renal failure). In this retrospective study, the need for ICU admission could be defined by using a rule that required the presence of either two of three minor criteria (systolic BP $\leq$ 90 mm Hg, multilobar disease, Pa_{O_2}/FI_{O_2} ratio $<$ 250) or one of two major criteria (need for mechanical ventilation or septic shock). When the other criteria for severe illness were evaluated, they did not add to the accuracy of predicting the need for ICU admission. With this rule the sensitivity was 78%, the specificity was 94%, the positive predictive value was 75%, and the negative predictive value was 95% (48).

Recommended Definition of Severe CAP and Need for ICU Admission

Although future prospective studies defining the need for ICU admission are still needed, the committee felt that severe CAP could be defined as the presence of two minor criteria (using only the three listed above or the five in the original ATS statement), or one major criterion (using the two listed above or the four in the original ATS statement) (*Level II evidence*). Other findings suggesting severe illness may also have utility, but have not been formally tested to define the need for ICU admission. These include the two (of the four) other criteria in the BTS rule (in addition to the two included in the definition of severe CAP), namely confusion and BUN $>$ 19.6 mg/dl.

TREATMENT GUIDELINES FOR COMMUNITY-ACQUIRED PNEUMONIA

Principles Underlying Antibiotic Therapy Recommendations

The purpose of these guidelines is to provide the practicing physician with a rational and manageable approach to the *initial antimicrobial management* of community-acquired pneumonia. By their very nature, these guidelines cannot encompass all eventualities. The approach chosen is a modification of the initial ATS guidelines, and is based, as shown in Tables 2–5, on an assessment of place of therapy (outpatient, hospital ward, or ICU), the presence of coexisting cardiopulmonary disease (chronic obstructive pulmonary disease, congestive heart failure), and the presence of modifying factors (Table 1). These modifying factors have been defined from published data and include the presence of risk factors for DRSP (age $>$ 65 yr, β-lactam therapy within 3 mo, alcoholism, multiple medical comorbidities, immunosuppressive illness or therapy, and exposure to a child in a day care center), the presence of risk factors for enteric gram-negatives (from a nursing home, underlying cardiopulmonary disease, underlying multiple medical comorbidities, and recent antibiotic therapy), and the presence of risk factors for *P. aeruginosa* (bronchiectasis, broad-spectrum antibiotic therapy for $>$ 7 d within the past month, malnutrition, and chronic corticosteroid therapy with $>$ 10 mg/d) (8, 52, 68). Patient stratification should be done without viewing age alone (in the absence of comorbid illness) as a predictor of enteric gram-negative infection. Therapy recommendations have incorporated the idea that atypical pathogen infection should be considered in all patient groups, sometimes in the form of mixed infection (*Level II evidence*). All patients fall into one of four groups (Figure 1), and each group is associated with a list of likely etiologic agents and suggested empiric therapy aimed at these potential pathogens (*Level II and III evidence*). The stratification of patients allows for a graded response in terms of the empiric therapy regimen selected. A less aggressive and narrower spectrum approach can be used for the milder cases, and as host factors become more complex or the severity of illness increases, a more aggressive and broad-spectrum regimen is recommended.

In using this approach, several principles should be considered. First, timing of initial therapy is important, because there are data showing a reduced mortality at 30 d if hospitalized patients receive their first dose of antibiotic therapy within 8 h of arrival at the hospital (77) (*Level II evidence*). In addition, it is desirable to give as narrow a spectrum of therapy as possible, avoiding excessively broad antibiotic therapy, if it is not needed. This goal is easily achieved if a specific etiologic diagnosis is made, but this is impossible in at least half of all patients, and the results of many diagnostic studies are not immediately available, making relatively broad spectrum empiric therapy a necessity for most patients, initially. Still, on the basis of epidemiologic considerations, even empiric therapy can be relatively narrow spectrum, provided that the patient does not have risk factors for DRSP or enteric gram-negatives (107, 108) (*Level I evidence*). For all patients, there is value in using initial empiric therapy based on guidelines. This type of approach not only assures timely therapy, but can also provide coverage for the possibility of mixed bacterial and atypical pathogen infection. Data in both outpatients and inpatients have shown that empiric therapy based on the initial ATS guidelines leads to a better outcome than if nonguideline therapy is used (55–57) (*Level II evidence*).

Several studies have attempted to validate treatment guidelines for CAP, for both outpatients and inpatients. Gleason and coworkers studied outpatients, and documented the value of macrolide monotherapy for patients $<$ age 60 yr and without comorbid illness, but also found that macrolide monotherapy was often effective for older patients with comorbid illness (55). Although this simple therapy, which was not recommended by the guidelines, was effective for some complex outpatients with comorbid illness, the findings did not necessarily negate the need for more broad-spectrum therapy in other outpatients with comorbid illness or advanced age. In the study, the patients who were treated according to the guidelines were few in number and were more severely ill than those treated with nonguideline therapy, and the therapy they received was primarily a β-lactam or trimethoprim/sulfamethoxizole alone, without the addition of a macrolide as recommended in Table 3 of the current guidelines. Gordon and coworkers examined nearly 4,500 patients admitted to the hospital and not the ICU, and found that therapy according to the guidelines (recommended β-lactam, with or without a macrolide) led to a lower mortality than if nonguideline recommended therapy was used, although the mortality was lowest for the patients who received a macrolide plus a β-lactam (57). In a Medicare study of nearly 13,000 patients, the use of a second- or third-generation cephalosporin with a macrolide (but not alone), or the use of a quinolone (primarily ciprofloxacin), were therapy regimens associated with reduced mortality, compared with all other regimens (56). These findings lend some credence to the potential importance of the role of atypical pathogens, and the need for routine therapy directed at this possibility, either by adding a macrolide to a β-lactam, or by using an antipneumococcal fluoroquinolone alone. Dean

and coworkers documented the value of a care process model based on the ATS guidelines, for providing appropriate antibiotic prescribing advice and for reducing hospital length of stay and cost (109, 109a).

Antimicrobial Choices

The fluoroquinolones have assumed an important role in the management of CAP because of the development of new agents with excellent antipneumococcal activity. The advantages of the antipneumococcal fluoroquinolones include the ability to cover gram-positive, gram-negative, and atypical pathogens with a single agent, generally given once a day (110). In addition, the newer agents have comparable MIC values for pneumococci that are either penicillin sensitive or penicillin resistant, although data have shown that high-level penicillin resistance can be associated with quinolone (ciprofloxacin) resistance (61). Quinolones penetrate well into the lung, often achieving levels higher than serum levels at sites such as the epithelial lining fluid and alveolar macrophages (110). In addition, quinolones are highly bioavailable, achieving similar serum levels with oral therapy as with intravenous therapy. These features allow for certain patients with moderately severe illness to be treated with oral therapy out of the hospital and also may permit the hospitalized patient to switch rapidly from intravenous to oral therapy, allowing for an early hospital discharge. There are some studies showing that admitted patients, even with bacteremia, can be effectively treated with an oral quinolone (111, 112). In spite of these data, it may be prudent to start all admitted patients who receive a quinolone on intravenous therapy to assure adequate blood levels (*Level III evidence*). Since anywhere from 10 to 20% of admitted patients do not respond to initial therapy (for a variety of reasons discussed below), it may be simpler to evaluate such individuals if there is no likelihood that the nonresponse is the result of a failure to absorb the initial therapy, as could occur if it was administered orally (113, 114).

Currently there are a number of new antipneumococcal fluoroquinolones available, or in development, for the therapy of CAP (110). Currently available agents (in addition to ciprofloxacin and ofloxacin) include levofloxacin, sparfloxacin, gatifloxacin, and moxifloxacin. Trovafloxacin is restricted globally because concerns about toxicity, and gemifloxacin is in development. Among the available and widely used new agents, only levofloxacin and gatifloxacin are currently available both intravenously and orally, while the other two agents are available only orally, but intravenous formulations of moxifloxacin and gemifloxacin are being developed. Drug-related toxicity has limited the usefulness of some of these agents, with some drugs having more class-related toxicities than others. These include photosensitivity (a particular problem with sparfloxacin) and gastrointestinal upset and neurotoxicity (seizures, lightheadedness). Severe liver toxicity has been reported with trovafloxacin, and as a result its use has been virtually halted. This effect, which can theoretically occur with any quinolone, seems more common with this particular agent, but was not evident in registration trials or in early clinical experience, suggesting the need to monitor all new agents for this possible effect (110, 115) (*Level III evidence*). Among the currently available agents, the MIC values for pneumococcus vary from 0.12 to 2.0 mg/dl, with the agents having antipneumococcal activity in the following order (most active to least active): moxifloxacin > gatifloxacin > sparfloxacin > levofloxacin (61,110). Gemifloxacin is more active *in vitro* against *S. pneumoniae* than moxifloxacin and gatifloxacin (61). Differences in the *in vitro* activity of these agents do not yet appear to have clinical impact, since all approved agents have documented efficacy in CAP (110, 115–117). The differences seen with *in vitro* activity may lead to different rates of resistance and clinical success in the future, if pneumococcal resistance to these agents becomes more common, but more data are needed.

The CDC has developed recommendations for empiric antibiotic therapy of CAP, if DRSP is likely (60). This statement emphasized the efficacy of older agents for the therapy of CAP, even in the presence of DRSP, and suggested that fluoroquinolones be considered as second choice agents for CAP, an opinion that the committee did not accept (*see below*). However, if DRSP is likely, the CDC group has identified a number of active β-lactam agents that can be used for initial empiric therapy, if the organism has a penicillin MIC of ⩽ 2 mg/L, which include oral therapy with cefuroxime (alternatively cefpodoxime), high-dose amoxicillin (1 g every 8 h), or amoxicillin/clavulanate (875 mg twice daily); intravenous therapy with cefotaxime, ceftriaxone, ampicillin/sulbactam; or, alternatively, a new antipneumococcal fluoroquinolone could be used (60) (*Level II and III evidence*). Other agents that are generally active *in vitro* against these organisms include cefepime, piperacillin/tazobactam, imipenem, and meropenem, but all of these agents are also active against *P. aeruginosa*, and are not recommended as primary therapy of CAP, since they provide broader coverage than is necessary, unless risk factors for *P. aeruginosa* are present (severe CAP, and some patients from nursing homes). If pneumococcal MIC values to penicillin are at 4 mg/L or greater, then the committee recommends that therapy should be with a new antipneumococcal fluoroquinolone, vancomycin, or clindamycin (*Level III evidence*). At the current time, all of the approved quinolones have efficacy in CAP and one agent, levofloxacin, is approved for CAP due to DRSP. However, in the future, it may be necessary to choose the most active quinolone (lowest pneumococcal MIC values) available, because data show that penicillin-resistant pneumococci can also be resistant to quinolones, particularly those agents with the highest MIC values (ciprofloxacin, levofloxacin), and preliminary reports of levofloxacin failures for pneumococcal pneumonia have appeared (61, 117, 118).

The committee felt that vancomycin should have a limited role, particularly for empiric therapy (60). If DRSP is suspected, other agents, as listed in Tables 2–5, will be effective, and vancomycin should be reserved for patients with high level resistance who are failing other therapies, or for those with suspected meningitis (*Level III evidence*). The empiric regimens for hospitalized patients do not specifically target *S. aureus*, but this pathogen should be considered in patients with CAP following influenza infection, and in those with a compatible sputum Gram's stain. Most of the initial therapy regimens are adequate against methicillin-sensitive *S. aureus*, and methicillin resistance is not common in CAP, making empiric vancomycin therapy unnecessary. However, in patients with severe CAP, coming from a nursing home known to harbor this organism, empiric vancomycin can be considered as part of initial empiric therapy. Several new therapies may have efficacy for CAP due to DRSP. Linezolid is available intravenously and orally and has efficacy against pneumococcus, including DRSP. The ketolides (the first agent being studied is telithromycin) have good *in vitro* activity against DRSP and may be an oral therapy option for outpatients at risk for infection with this organism.

Although high rates (up to 61%) of *in vitro* macrolide resistance can coexist with penicillin resistance, there are few reports of macrolide failures in CAP due to drug-resistant pneumococci and these agents should be effective for organisms with penicillin MIC values of ⩾ 2.0 mg/L (60a, 119). This may

be the result of the high degree of macrolide penetration into respiratory secretions, and other relevant tissue sites of infection. In addition, most macrolide resistance in North America (but not all parts of Europe) is due to an efflux mechanism, and not a ribosomal mechanism, with the efflux mechanism being associated with substantially lower MIC values than the ribosomal mechanism (119). In addition, in the regimens listed in Tables 2–5, macrolides are used alone only in the absence of risks for DRSP and enteric gram-negatives, and if these risks are present, macrolides are used as part of a combination regimen with one of the β-lactams that is highly active against DRSP. There have been case reports of a few patients with macrolide-resistant pneumococcal bacteremia requiring hospitalization after oral therapy with a macrolide, but most of these patients would not have been candidates for macrolide monotherapy, according to the recommendations in Tables 2–4, and some of these patients received this oral therapy for nonpneumonia indications (119a–119c).

Certain agents that should *not* be used if DRSP is suspected, because of a possible lack of efficacy, include first-generation cephalosporins, cefaclor, loracarbef, and trimethoprim/sulfamethoxizole.

Therapy Recommendations

In each patient category listed in Tables 2–5, the committee has recommended specific therapy options. In each category, several choices for empiric therapy have been provided, and when possible, the committee recommended a more narrow-spectrum empiric therapy, such as a macrolide alone, particularly if the patient has no risks for DRSP, aspiration, or enteric gram-negatives (107, 108). In Tables 2–5 there are multiple alternative therapies, and if there is no particular order of preference, this is stated in tables. For more complex patients, the scheme usually involves the choice between a β-lactam/macrolide combination or monotherapy with a new antipneumococcal fluoroquinolone. Clinical studies have shown that either approach is effective and safe, and it is unclear that there is an advantage to choosing one regimen over another (*Level II evidence*). The members of the consensus panel recommend that when choosing between these options, physicians consider using both approaches in different patients, in order to avoid the selection pressure for resistance that would follow from using one antibiotic approach for all patients. This recommendation (*Level III evidence*) has not been tested and needs further study.

Outpatient therapy. If the patient has no cardiopulmonary disease, and no risks for DRSP, aspiration, or enteric gram-negatives, then the likely organisms will be pneumococcus, atypical pathogens, respiratory viruses, and possibly *H. influenzae* (especially in cigarette smokers). For these patients (Group I, Table 2) therapy should be with an advanced generation macrolide, with doxycycline as a second choice (because of less reliable activity against pneumococcus) for patients who are allergic or intolerant of macrolides. The committee felt that broader spectrum coverage with a new antipneumococcal fluoroquinolone would be effective, but unnecessary, and if used in this setting could promote overusage of this valuable class of antibiotics (*Level III evidence*). If *H. influenzae* is not likely, because the patient is a nonsmoker without cardiopulmonary disease, any macrolide could be used, including erythromycin. However, the advanced generation macrolides (azithromycin, clarithromycin) have a lower incidence of gastrointestinal side effects than erythromycin and are administered less frequently (once or twice daily) than erythromycin, improving the likelihood of patient compliance with therapy (120). Although clarithromycin is not as active *in vitro* against *H. influenzae* as azithromycin, clinical experience with both azithromycin and clarithromycin in CAP has been favorable. This may be explained by the excellent concentrations of macrolides achieved in the epithelilal lining fluid and alveolar macrophages, and by the predominance of the efflux mechanism of pneumococcal resistance in North America.

The more complex outpatient (Group II, Table 3) can be managed with either a β-lactam/macrolide combination or monotherapy with an antipneumococcal fluoroquinolone (*Level II evidence*). Doxycycline can be used, along with a β-lactam, as an alternative to a macrolide for these patients. For many patients, the ease of using one drug once daily will make the quinolone option more appealing, and in some instances less expensive. The oral β-lactam should be one of the agents that is likely to be effective if DRSP is present (listed in Table 3 and above), and the agent should be used in an adequate dose, as discussed above. If ampicillin is used, it does not provide adequate coverage of *H. influenzae*, and thus should be combined with either an advanced generation macrolide (not erythromycin) or doxycycline. One β-lactam option that can be used is parenteral (intravenous or intramuscular) once-daily ceftriaxone along with a macrolide or doxycycline. The parenteral β-lactam can be switched to oral therapy after 1–2 d, provided the patient is showing an appropriate clinical response. If the patient has aspiration risk factors, or is living in a nursing home, anaerobes should be covered and this can be achieved with amoxicillin/clavulanate or amoxicillin (still combined with a macrolide). If anaerobes are documented, or if a lung abscess is present, clindamycin or metronidazole should be incorporated into the therapy regimen.

Inpatient therapy. For the admitted patient with cardiopulmonary disease, and/or risk factors for DRSP or enteric gram-negatives, therapy can be with either a β-lactam/macrolide combination or monotherapy with an antipneumococcal fluoroquinolone (Group IIIa, Table 4a) (*Level II evidence*). If risks for DRSP are present, the β-lactam should be one of the selected agents listed above. When a β-lactam is used in these patients, it is not used alone, but combined with a macrolide to provide coverage for atypical pathogen infection (*Level II evidence*). The macrolide can be given either orally or intravenously, depending on the severity of illness of the patient (121). Doxycycline can be used for the patient who is allergic or intolerant to macrolides. If the patient has risk factors for aspiration, or is living in a nursing home, anaerobes should be covered by using either ampicillin/sulbactam, high-dose ampicillin, or other active β-lactams. For the admitted patient, if anaerobes are documented, or if a lung abscess is present, clindamycin or metronidazole should be added to the regimen.

For the admitted patient not in the ICU, without risks for DRSP or enteric gram-negatives and without cardiopulmonary disease (Group IIIb, Table 4b), there are data to suggest the efficacy of intravenous azithromycin alone; however, few admitted patients are likely to fall into this category (*Level II evidence*). The dose of intravenous azithromycin is 500 mg daily for 2–5 d, followed by oral therapy at 500 mg daily for a total of 7–10 d, and this therapy has been effective for admitted patients with CAP, including those with pneumococcal bacteremia (107, 108). If the patient is macrolide allergic or intolerant, then therapy should be with doxycycline and a β-lactam, or with an antipneumococcal fluoroquinolone alone. Although one study has reported that doxycycline is a cost-effective monotherapy for admitted patients with CAP (122), the study has many limitations, and the committee did not feel that this monotherapy option should be used. In addition, there was concern that with widespread use, pneumococcal resistance could emerge more rapidly to doxycycline than to

other agents, and the photosensitivity associated with this agent may limit its use in some geographic areas.

For the patient with severe illness, therapy should be directed against pneumococcus, *Legionella* (and other atypicals), and *H. influenzae*, but patients should be stratified on the basis of whether risks for *P. aeruginosa* are absent or present (Group IVa, Table 5a; and Group IVb, Table 5b) (*Level III evidence*). In the absence of pseudomonal risk factors, therapy should be with a β-lactam that would be active against DRSP plus either azithromycin or a quinolone (Group IVa, Table 5a). Erythromycin was not recommended for this group because of difficulties in administration and tolerance. When a β-lactam is used in this population (Group IVa, Table 5a) and in the patients included in Group IIIa, (Table 4a), the agent should be active against DRSP, but agents that are also active against *P. aeruginosa* (cefepime, piperacillin/tazobactam, imipenem, meropenem) are not recommended as primary therapy when this organism is not suspected (*Level III evidence*). The role of antipneumococcal fluoroquinolone monotherapy in severe CAP is currently uncertain. The published clinical trials have generally involved few patients admitted to the ICU, and the proper dosing and efficacy of the new quinolones for severe CAP is unknown. There are data with ciprofloxacin (400 mg every 8 h) showing efficacy in severe CAP, but the number of patients studied is small (123). Until more data become available, the committee suggests that if quinolones are used for severe CAP, they be used as a replacement for a macrolide, and be part of a combination regimen, usually with a β-lactam (*Level III evidence*). The addition of a β-lactam will also assure adequate therapy of pneumonia complicated by meningitis, since the efficacy of quinolone monotherapy in this setting is unknown. If pseudomonal risk factors are present (Group IVb, Table 5b), therapy should include two antipseudomonal agents, and provide coverage for DRSP and *Legionella*. This can be done with selected β-lactams (cefepime, piperacillin/tazobactam, imipenem, meropenem) plus an antipseudomonal quinolone (ciprofloxacin), or with selected β-lactams plus an aminoglycoside and either azithromycin or a nonpseudomonal quinolone (*Level III evidence*). If the patient is at risk for *P. aeruginosa* and is also β-lactam allergic, aztreonam can be used in place of the β-lactams listed above, and should be combined with a regimen that includes an aminoglycoside and an antipneumococcal fluoroquinolone.

DURATION OF THERAPY, RESPONSE TO THERAPY, AND SWITCH TO ORAL THERAPY

Duration of Treatment

Surprisingly few data exist to define the optimal duration of therapy for CAP and standard textbooks provide little specific referenced information about this issue. In the past, standard therapy has been 7–14 d, but new agents with a long serum or tissue half-life have been developed, which shorten the duration of drug administration. Clinical trials are being conducted with old and new agents to examine the optimal duration of therapy in both inpatient and outpatient settings. Studies are being designed to examine courses of therapy for 5–7 d among outpatients, and for 7–10 d for inpatients (124). Short treatment courses may also be possible with the 15-member macrolide, azithromycin. This agent has a half-life of 11 to 14 h, compared with 1.5 to 3 and 3.8 h for erythromycin and clarithromycin, respectively (120). Azithromycin remains in the tissues longer than most agents, so that reduced length of treatment based on the number of days of oral ingestion of the drug is misleading. Trials comparing oral azithromycin for 5 d with erythromycin and with cefaclor for 10 d in the treatment of pneumonia due to "atypical pathogens" and bacterial pathogens, respectively, suggest that shorter courses with this agent may be used (125, 126). Trials of intravenous azithromycin in CAP have reported a duration of therapy of 7–10 d, while 7 d of therapy may be possible with some of the new antipneumococcal fluoroquinolones (107, 108, 110, 116, 117).

Recommendations. The presence of coexisting illness and/or bacteremia, the severity of illness at the onset of antibiotic therapy, and the subsequent hospital course should be considered in determining the duration of antibiotic therapy. Generally, *S. pneumoniae* pneumonia, and other bacterial infections, should be treated for 7 to 10 d, and there are no data showing that a longer duration of therapy is needed for bacteremic patients, provided that the patient has had a good clinical response. Patients with *M. pneumoniae* and *C. pneumoniae* may need longer therapy ranging from 10 to 14 d. Immunocompetent patients with Legionnaire's disease should receive treatment for 10–14 d, whereas patients chronically treated with corticosteroids may require 14 d, or longer, of therapy (*Level III evidence*).

Expected Clinical Course and Response to Therapy

Duration of therapy and the early switch to oral therapy for hospitalized patients are decisions that are based on patients responding to therapy in an expected and appropriate fashion. Failure to respond as expected should lead to other diagnostic and therapeutic considerations (*see below*). The expected response of the hospitalized patient with CAP falls into three different periods: the first, starting with the initiation of appropriate parenteral therapy, lasts 24–72 h and during this time the patient becomes progressively more clinically stable; the second period typically starts by Day 3, with the patient having clinical stability demonstrated by improvement in signs, symptoms, and laboratory values; the third period is one of recovery and resolution of abnormal findings. Delay in the onset of clinical improvement can result from host or pathogen factors, and at any point clinical deterioration can occur. In general, with increasing patient age, multiple coexisting illnesses, and increasing severity of disease, the resolution of clinical signs and symptoms will be delayed (*Level II evidence*) (127–133). Other factors associated with delayed resolution include alcoholism, multilobar pneumonia, and bacteremia (127,128). Clinical deterioration usually occurs early, within the first 3 d, and a pattern of improvement and then deterioration is unusual and often the result of deep-seated infection (empyema) or an intercurrent process.

In individuals who are otherwise healthy, fever can last for 2–4 d, with defervescence occurring most rapidly with *S. pneumoniae* infection, and slower with other etiologies (21, 129, 130). Leukocytosis usually resolves by Day 4, while abnormal physical findings (crackles) persist beyond 7 d in 20–40% of patients. Abnormal findings on chest radiograph clear more slowly than do clinical signs of pneumonia. For those less than 50 yr old, and otherwise healthy, *S. pneumoniae* pneumonia will clear radiographically by 4 wk in only 60% of patients (128,131). If the patient is older, has bacteremic pneumonia, COPD, alcoholism, or underlying chronic illness, radiographic clearing is even slower, and only 25% will have a normal radiograph at 4 wk (131). *Mycoplasma pneumoniae* infection can clear radiographically more rapidly than pneumococcal infection, while pneumonia due to *Legionella* sp. will clear more slowly (94).

The radiograph often worsens initially after therapy is started, with progression of the infiltrate and/or development of a pleural effusion. If the patient has mild or moderate pneumonia or is showing an otherwise good clinical response, this

radiographic progression may have no significance. However, radiographic deterioration in the setting of severe community-acquired pneumonia has been noted to be a particularly poor prognostic feature, highly predictive of mortality (8).

Recommendations for management based on clinical response. On the basis of the clinical response to therapy, patients may be categorized into three groups: (*1*) patients with early clinical response; (*2*) patients with lack of clinical response, which should be defined at Day 3 of hospitalization; and (*3*) patients with clinical deterioration, which can occur as early as after 24–48 h of therapy. Those falling in the first category should be considered for rapid switch to oral therapy, followed by prompt hospital discharge (*Level II evidence*). Patients in the second and third categories need an evaluation of host and pathogen factors, along with a reevaluation of the initial diagnosis and a search for complications of pneumonia and pneumonia therapy (*see below*). Because of the natural course of treatment response, antibiotic therapy should not be changed within the first 72 h, unless there is marked clinical deterioration or if bacteriologic data necessitate a change (*Level III evidence*) (132, 132a). In the setting of severe pneumonia, radiographic deterioration, along with accompanying clinical deterioration, may signify inadequately treated infection, and thus aggressive evaluation and a change in antimicrobial therapy may be necessary, even before 72 h of therapy has elapsed (*Level III evidence*).

When to Consider Switch to Oral Therapy

The decision to switch from intravenous to oral antibiotic therapy is based on an assessment of clinical response, evaluating symptoms of cough, sputum production, dyspnea, fever, and leukocytosis. Once the patient has clinically stabilized, switch to oral therapy can be achieved, and up to half of all patients are eligible on hospital Day 3 (132). Some studies have shown that early switch to oral therapy can reduce hospital length of stay, and may even improve outcome, compared with prolonged intravenous therapy (132, 132a). If the patient meets appropriate criteria for switch therapy, oral antibiotics can be started, even if the patient had a positive blood culture (133). Bacteremic patients may take longer to meet criteria for switch therapy than nonbacteremic patients, but once criteria are met the switch can be safely accomplished, unless the organism is *S. aureus*, in which case the patients need a longer duration of therapy to prevent or treat endocarditis.

Another issue to consider is whether it is necessary to maintain the same drug levels with oral therapy as were achieved with intravenous therapy. Agents that achieve comparable serum levels either intravenously or orally, defined as "sequential" therapy, include doxycycline, linezolid, and most quinolones (120). With the β-lactams (penicillin, cephalosporins) and macrolides, the switch to oral therapy is associated with a decrease in serum levels, compared with intravenous therapy, and this is defined as "step-down" therapy. Good clinical success has been documented with either a sequential or a step-down approach (124, 132).

Recommendations. Patients should be switched to oral therapy if they meet four criteria: improvement in cough and dyspnea, afebrile ($< 100^\circ$ F) on two occasions 8 h apart, white blood cell count decreasing, functioning gastrointestinal tract with adequate oral intake (132, 132a). However, if the overall clinical response is otherwise favorable, it may not be necessary to wait until the patient is afebrile before making the switch to oral therapy (*Level II evidence*) (132a, 133). In selecting an oral antibiotic for switch therapy, a specific agent, based on organism sensitivity patterns, can be chosen if the etiologic pathogen is known. In this instance the narrowest spectrum agent with an appropriate pharmacokinetic profile should be chosen; however, the issue of possible atypical pathogen coinfection should be considered. In most instances, a specific pathogen is not identified and the oral therapy should continue the spectrum of the intravenous agents used (*Level III evidence*). Compliance is a key issue with oral therapy and thus agents should be chosen with a minimum of side effects, and with dosing either once or twice daily, factors that increase the likelihood that the patient will complete a full course of therapy (134). Patients should also be instructed to avoid potential drug–drug interactions and to avoid antacids and certain foods that could interfere with drug absorption.

Hospital Discharge

Patients who reach clinical stability for their pneumonia and are switched to oral therapy may still require hospitalization because of unstable coexisting illnesses, such as diabetes or congestive heart failure. Patients may also need therapy for life-threatening complications such as cardiac arrhythmia, and for management of social needs, such as an unstable home situation (135, 136).

A repeat chest radiograph early in the hospital stay is unlikely to show marked improvement, even if the patient has a good clinical response. Some patients may have an abnormal chest radiograph due to slow radiographic clearing, without clinical significance, but radiographs should be followed until a new stable baseline is achieved (128). An evaluation is needed if the chest radiograph fails to return to normal, especially in a patient without complete resolution of clinical signs and symptoms (138).

Recommendations. In the absence of any unstable coexisting illnesses, or other life-threatening complications, the patient should be discharged home the same day that clinical stability occurs and oral therapy is initiated. In-hospital observation on oral therapy is not necessary, and only adds to cost and length of stay, without any measurable clinical benefit (*Level II evidence*) (132a, 136). There is no need to repeat a chest radiograph prior to hospital discharge in a patient who is clinically improving. A repeat radiograph is recommended during a follow-up office visit, approximately 4 to 6 wk after hospital discharge, to establish a new radiographic baseline and to exclude the possibility of malignancy associated with CAP, particularly in older smokers (128, 137) (*Level III evidence*).

MANAGEMENT OF PATIENTS WHO DO NOT RESPOND ADEQUATELY TO INITIAL THERAPY

If the patient's clinical findings are not improving or are deteriorating after initial empiric therapy, consideration must be given to several possible causes. If the patient is not clinically stable by Day 3, and if host factors associated with a delayed response are present, continued therapy, without an antibiotic change, is appropriate. If, however, the patient has no explanation for a slow response, if there is no response after 7 d of therapy, or if there is clinical deterioration after 24 h of therapy, a careful re-evaluation to identify treatable causes is necessary (*Level III evidence*). The common etiologies for clinical deterioration fall into the following four categories.

Inadequate Antimicrobial Selection

The etiologic organism may be resistant to the drug(s) used in the initial empiric regimen (i.e., not covered by the initial antibiotic therapy). For example, the therapies outlined above are not optimal for *S. aureus*, and an aggressive search for this pathogen should be undertaken in the patient who worsens on the above-described regimens. Although empiric therapy for

DRSP is recommended only for patients with risk factors, it is possible for a patient without identified risk factors to be infected with DRSP and fail to respond to empiric therapy with a recommended regimen. If the patient has risk factors for *P. aeruginosa*, this organism may fail to respond to a recommended empiric therapy regimen. Alternatively, the infection could be caused by an agent that is not responsive to antimicrobials of any type (i.e., a virus). Another possible explanation is that the responsible pathogen was initially sensitive to the antibiotics used, but has now become resistant, and thus organism sensitivities on both the initial (if obtained) and repeat sputum cultures should be checked.

Unusual Pathogens

An additional consideration is that the patient may have community-acquired pneumonia caused by an unusual organism. Such infections should be considered when clinical and radiographic findings persist (chronic pneumonia), and the differential diagnosis includes tuberculosis, endemic fungal pneumonia (such as coccidioidomycosis), and *P. carinii* pneumonia. In addition, some patients may have a "relapsing" pneumonia, which appears to improve and then deteriorates. This situation should lead to consideration of unusual pathogens, including tuberculosis and nocardiosis. Although a discussion of the immunocompromised and/or HIV-infected patient is not included in this statement, it is possible that a patient will have one of these conditions, even though this was not initially suspected. Patients who receive corticosteroids have been reported to develop community-acquired fungal pneumonia (139).

A careful repeat of the history is essential in the patient who is not improving, and certain epidemiological clues related to animal exposures and travel may suggest specific pathogens that can be detected with special serologies or cultures (Table 6). Q fever (*C. burnetii*) may follow exposure to parturient cats, cattle, sheep, or goats. Tularemia can occur with exposure to infected rabbits, and ticks. Psittacosis may occur after exposure to avian sources of infection; and plague or leptospirosis can follow exposure to rats. Anaerobes due to aspiration should be considered if the patient has a history of alcoholism, injection drug use, nursing home residency, neurologic illness, or any other cause of impaired consciousness. Travel to Southeast Asia can be complicated by infection with *Burkholderia* (*Pseudomonas*) *pseudomallei*, while Paragonimiasis can be acquired in Asia, Africa, or Central and South America. A history of tuberculosis exposure and prior tuberculin skin test status should also be elicited. If the skin test for tuberculosis has not been done and the patient is in an epidemiological risk group, it should be applied, and sputum collected for tuberculosis staining and culture. Other unusual pathogens that can lead to a syndrome of CAP include mycobacteria other than tuberculosis, endemic fungi (histoplasmosis, coccidioidomycosis, blastomycosis), *Pasteurella multocida*, *Bacillus anthracis*, *Actinomyces israeli*, *Francisella tularensis*, *Leptospira* spp., Nocardia spp, *Rhodococcus equi*, *Yersinia pestis* (plague), and hantavirus.

Complications of Pneumonia

In addition to the diagnoses considered above, the patient who remains ill in spite of empiric therapy may have extrapulmonary complications of pneumonia. Up to 10% of patients with bacteremic pneumococcal pneumonia can have metastatic infections, which include meningitis, arthritis, endocarditis, pericarditis, peritonitis, and empyema (140). Particularly because of concern about empyema, any patient with an inadequate clinical response to therapy should have a repeat chest radiograph, and possibly a CT scan, and any pleural fluid should be sampled, cultured, and analyzed for cell count and chemistry. A CT scan can also support the diagnosis of the presence of a lung abscess, which can complicate certain forms of pneumonia. A spinal fluid examination or echocardiogram may be necessary to rule out meningitis or endocarditis. In addition to metastatic infection, several noninfectious extrapulmonary complications of pneumonia can delay radiographic clearing. These include renal failure, heart failure, pulmonary embolus with infarction, and acute myocardial infarction. Finally, if the patient has developed severe sepsis from pneumonia, the chest radiograph and clinical course may deteriorate because of the presence of acute respiratory distress syndrome (ARDS) and multiple system organ failure. A late complication of CAP, nosocomial pneumonia, can also complicate the illness and lead to an apparent nonresponse to therapy.

Noninfectious Illness

A final consideration is the group of noninfectious diseases that can mimic pneumonia and initially be misdiagnosed as infection. These include pulmonary embolus, congestive heart failure, obstructing bronchogenic carcinoma, lymphoma, intrapulmonary hemorrhage, and certain inflammatory lung diseases (bronchiolitis obliterans and organizing pneumonia, Wegener's granulomatosis, sarcoidosis, hypersensitivity pneumonitis, acute interstitial pneumonitis, drug-induced lung disease, and eosinophilic pneumonia).

Evaluation and Testing

When a patient is not improving after initial empiric therapy, it is necessary to consider the value of certain tests for a patient who is already taking antibiotics. For example, nonresponse while receiving antibiotic therapy may indicate the possibility that a resistant, or superinfecting, pathogen is present. However, antibiotics can also decrease the utility of invasive diagnostic methods such as bronchoscopy, which has a high false-negative rate when performed while the patient is receiving antibiotics, although if organisms are recovered by this method, they are often resistant to current antibiotic therapy (141).

One study examined the utility of bronchoscopy in patients who failed empiric therapy for community-acquired pneumonia (142). Therapeutic failures were defined as early (no clinical response within 72 h) or late (initial improvement, but deterioration after 72 h). The incidence of such failures was relatively low, 6.5% of 277 patients having early failure, and 7% having late failure. Bronchoscopy was done when failure occurred, and provided diagnostically useful information in 41% of cases. Bronchoscopy, even in the presence of antibiotics, led to such diagnoses as *Legionella* sp. infection, anaerobic pneumonia, infection with resistant or unusual pathogens, and tuberculosis. In addition, bronchoscopy can diagnose other infections, including those caused by fungi and *P. carinii*, and it may be useful in detecting mechanical factors that are delaying resolution, such as an aspirated, obstructing foreign body or an obstructing endobronchial lesion. Another study evaluated the utility of bronchoscopy in patients with persistent radiographic and clinical abnormalities (138). In that study, bronchoscopy did yield specific diagnoses, but this occurred primarily in nonsmoking patients, less than age 55 yr, who had multilobar infiltrates of long duration. Those who were older, those who have smoked, and those with focal infiltrates had a much lower yield of a specific diagnosis (other than slowly resolving pneumonia) with fiberoptic bronchoscopy.

An open lung biopsy is most useful for defining noninfectious processes in the immunocompetent patient, but may also detect tuberculosis, fungal infections, and other infectious causes. Fortunately, in the setting of CAP, open lung biopsy is rarely needed, and in one study was shown to generally provide little information to improve patient outcome (143).

Recommendations for Evaluating the Nonresponding Patient

Bronchoscopy is usually not needed, and patience is necessary to observe the full course of radiographic clearing of community-acquired pneumonia (*Level III evidence*). However, bronchoscopy should be considered in patients below the age of 55 yr, who have multilobar disease and are nonsmokers. If bronchoscopy is performed, the goal is to identify unusual organisms or drug-resistant pathogens, but the clinician could also obtain this information by collecting lower respiratory tract secretions (sputum or endotracheal aspirate) for culture. Cultures should be sent to evaluate for drug-resistant and unusual pathogens, including tuberculosis.

In addition to sampling lower respiratory tract secretions, other tests should be considered. Computed tomography may reveal unsuspected collections of pleural fluid, multiple lung nodules, or cavitation within a lung infiltrate. Lung scanning, spiral CT scanning, and/or pulmonary angiography should be considered if the patient is at risk for pulmonary embolus with infarction. While the routine use of serologic testing is not useful in the initial evaluation of patients with community-acquired pneumonia, serologic tests for *Legionella* sp., *Mycoplasma pneumoniae*, viral agents, endemic fungi, and other unusual pathogens should be considered at this point. *Legionella* urinary antigen testing should also be considered. This test is positive in more than half of all patients with proven *Legionella pneumophila* infection, and more than 80% of patients with *Legionella pneumophila* serogroup 1 infection (81, 82).

If this extensive diagnostic evaluation has not been useful, and if the patient is seriously ill, open lung biopsy of an involved area of lung should be considered (*Level III evidence*).

VACCINATION RECOMMENDATIONS FOR THE PATIENT AT RISK FOR COMMUNITY-ACQUIRED PNEUMONIA

Appropriate patients at risk for CAP should be vaccinated with both pneumococcal and influenza vaccine, both of which have been shown to be safe and effective (*Level I and II evidence*). Cigarette smoking is a risk factor for pneumonia, and smoking cessation, particularly in patients who have had pneumonia, remains an important preventive strategy for CAP.

Pneumococcal Vaccine

The current vaccine contains the purified capsular polysaccharide from the 23 serotypes that cause 85–90% of the invasive pneumococcal infections in adults and children in the United States (144). Both Pneumovax and PneuImmune are effective in preventing invasive illness (bacteremia, meningitis, or infection of other normally sterile sites) caused by the included serotypes. The vaccine is both cost-effective and potentially cost saving among individuals over the age of 65 yr for the prevention of bacteremia (145, 146). Efficacy has been inconsistently demonstrated in placebo-controlled trials in patients with chronic illness, but the case-control methodology has documented effectiveness in the range of 56–81% (147–149). Efficacy has also been documented by serotype prevalence studies for bacteremic illness, but not for nonbacteremic pneumonia. The benefits of vaccination have been shown in specific patient groups, and have ranged from 65 to 84% effectiveness in such populations as persons with diabetes mellitus, coronary artery disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia (148, 149). In immunocompetent patients over the age of 65 yr, effectiveness has been documented to be 75%. In the immunocompromised patient, effectiveness has not been proven, and this includes patients with sickle cell disease, chronic renal failure, immunoglobulin deficiency, Hodgkin's disease, lymphoma, leukemia, and multiple myeloma (148, 149).

The vaccine in its current form leads to an antibody response that declines over 5–10 yr. When the vaccine is given, approximately half of all patients develop mild, local side effects such as pain at the injection site, erythema, and swelling, which last for less than 48 h. Moderate systemic reactions such as fever and myalgia are uncommon, as are more severe local reactions (local induration). No episodes of neurologic illness (Guillain–Barré syndrome) have been reported with the vaccine. A transient increase in HIV replication, of unknown significance, can occur after vaccination in HIV-infected persons. A new conjugated polysaccharide vaccine has been licensed for children. It induces a T cell-dependent response that leads to more prolonged immunologic memory.

Recommendations for use. All immune-competent patients aged 65 yr or greater should be immunized (149, 150). Persons age 64 yr or less should be immunized if they have chronic illnesses, such as cardiovascular disease (congestive heart failure), chronic pulmonary disease (COPD, but not asthma), diabetes mellitus, alcoholism, chronic liver disease (cirrhosis), cerebrospinal fluid leaks, and functional or anatomic asplenia; or if they are living in special environments or social settings (Alaskan natives, certain American Indian populations, those in long-term care facilities) (*Level II evidence*). To facilitate these recommendations, persons over age 50 yr should have their vaccination status and risk factors reviewed when they see their primary care physician.

The efficacy in immunosuppressed patients is less certain, although we recommend that vaccination be given to these populations, which include persons with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephrotic syndrome, and persons receiving immunosuppressive therapy (including long-term steroids). If immunosuppressive therapy is being contemplated, vaccination should be given at least 2 wk before, if possible.

A single revaccination is indicated in a person who is age $\geq$ 65 yr who initially received the vaccine $>$ 5 yr earlier and was $<$ age 65 yr of age on first vaccination. If the initial vaccination was given at age 65 yr or older, a repeat is not indicated. If the patient has anatomic or functional asplenia, revaccination is indicated if the patient is $>$ 10 yr of age and the second dose is given at least 5 yr after the original dose. In the immunocompromised patient populations listed above, a repeat vaccination after 5 yr is also indicated.

To improve the rate of vaccination, evaluation of candidates should occur in health care provider offices, in outpatient clinics, and in the hospital prior to discharge for virtually any medical illness. Hospital-based immunization for most admitted patients could be highly effective, since more than 60% of all patients with CAP have been admitted to the hospital, for some indication, in the preceding 4 yr, and hospitalization could be defined as an appropriate time for vaccination (151, 152) (*Level III evidence*). Pneumococcal vaccine can be given simultaneously with other vaccines such as influenza vaccine, but each should be given at a separate site.

The Health Care Financing Agency has approved the use of standing orders to give the vaccine to Medicare patients, and roster billing has been authorized since August 1996. The codes used for vaccination include V03.82, the diagnostic code for *Streptococcus pneumoniae*; 90732, the CPT code for pneumococcal vaccination; and G0009, the HCPCS Level II code for administering pneumococal vaccination. The newly licensed protein-conjugated pneumococcal vaccine (Prenevar) contains only seven serotypes. It is protective against most of the serotypes that cause otitis media, pneumonia, and meningitis in children. It is now universally recommended for

healthy children beginning at age 2 mo (152a). It has not been adequately tested in adults. The older polysaccharide vaccine can be used in at-risk children beginning at 2 yr of age.

Influenza Vaccine

Influenza occurs in epidemic fashion, and between 1972 and 1992 there have been > 20,000 influenza-associated deaths in each of nine epidemics (153). During the same period, four of these epidemics resulted in > 40,000 influenza-associated deaths. The influenza vaccine is modified annually to reflect the anticipated strains in the upcoming season, and the current vaccine contains three strains of virus: an influenza A strain (H3N2), an influenza A strain (H1N1), and an influenza B strain. The vaccine virus is grown in eggs, purified, and then inactivated, so that it is noninfectious and cannot lead to clinical infection. In adults the vaccine can be a split virus vaccine (subvirion and purified surface antigens) or a whole virus vaccine. The current manufacturers are Connaught Laboratories, Evans Medical, and Wyeth Ayerst.

The vaccine has been shown to be effective in preventing or attenuating illness in the elderly and in younger individuals, with efficacy depending on the match between the vaccine strain and the circulating strain (154–156). When the match is good, the vaccine can prevent illness in 70–90% of healthy persons aged < 65 yr. For elderly persons with certain chronic illnesses, the efficacy is less, but the vaccine can still attenuate the influenza infection, leading to less frequent lower respiratory infections and the associated morbidity and mortality that follow influenza infection. Although the vaccine is less effective for older persons than for younger persons, it can prevent severe illness and death. In one meta-analysis of 20 studies, the vaccine was shown to reduce the occurrence of pneumonia by 53%, hospitalization by 50%, and mortality by 68% (154). In addition, the vaccine has been shown to reduce all-cause mortality during influenza season by 27–54% (155, 156), and has been shown to be cost-effective in multiple studies (156).

Concern about side effects has limited the use of the vaccine by some patients, but the vaccine does not contain live virus and cannot lead to influenza. Reactions include local soreness at the injection site, which may last up to 2 d, and is generally mild and not disabling; systemic symptoms of fever, malaise, and myalgias beginning 6–12 h after vaccination and lasting for 1–2 d, which are not more common than with placebo (157); rare immediate allergic reactions in patients with egg hypersensitivity; and Guillain–Barré syndrome, which has been clearly associated only with the 1976 swine influenza vaccine and has not been associated with other vaccines since then (158).

Recommendations for use. Target groups include those at increased risk for influenza complications, those who can transmit influenza to high-risk patients, and other special groups including any person who wishes to reduce the chance of becoming infected with influenza (159) (*Level I evidence*).

Groups at increased risk for influenza-related complications are persons > 65 yr, residents of nursing homes or chronic care facilities, patients with chronic pulmonary or cardiovascular disease, those who required regular medical care or hospitalization in the preceding year (for diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression), and pregnant women in the second or third trimester during influenza season.

Those who can transmit the illness to high-risk individuals include physicians, nurses, and other personnel in the hospital or outpatient setting; employees of nursing homes and chronic care facilities; home care providers for high-risk patients, and household members of patients in the above high risk groups. Other special groups who should consider vaccination include persons with HIV infection, breast-feeding mothers, travelers to foreign countries during influenza epidemics, those who provide essential community services, and persons who study or work in institutional settings.

Since the relevant viral strain changes annually, revaccination is needed yearly, and should be given from the beginning of September through mid-November. Vaccination can be cost-effective if given to at-risk individuals during hospitalization or during routine health care, before the influenza season. Roster billing can be used in the hospital or in physician's offices, and the following billing codes can be used: V04.8, the diagnostic code for influenza virus; 90724, the CPT code for influenza virus vaccine; and G0008, the HCPCS Level II code for administering influenza virus vaccine. Vaccine programs can facilitate delivery of the vaccine and should be developed in outpatient clinics, emergency rooms, and walk-in clinics, nursing homes, outpatient facilities providing care to high-risk patients (dialysis centers), home care programs, traveler's clinics, and other health care facilities.

A new, live attenuated virus vaccine has been shown to be safe and effective in children as well as healthy working adults.

Antiviral Therapy and Chemoprophylaxis

The older available antiviral agents (amantadine and rimantadine) are active against influenza A virus, but not influenza B virus, while the new neuraminidase inhibitors—zanamivir and oseltamivir—are active against both influenza A and B (160–162).

Amantadine and rimantadine can be given as therapy for influenza and can reduce the severity and duration of illness if administered within 48 h of the onset of symptoms, but their impact on preventing influenza-related complications in high-risk patients is uncertain. These agents can be used during an institutional outbreak of influenza to treat infected persons and to serve as prophylaxis for unvaccinated individuals, and therapy is continued for 1 wk after the end of the outbreak.

Antiviral prophylaxis is 70–90% effective against influenza A virus, using either amantadine or rimantadine for the duration of the epidemic in the community (160). Targets for prophylaxis are high-risk patients who have been vaccinated after the onset of the epidemic (they are treated for 2 wk only); persons caring for high-risk patients; persons with immune deficiency; persons in whom the vaccine is contraindicated; and others desiring prophylaxis of influenza A illness.

Adverse reactions to amantadine include central nervous system effects (nervousness, anxiety, difficulty concentrating, lightheadedness), and gastrointestinal side effects (nausea, anorexia). The incidence of central nervous system side effects is less with rimantadine. Dosage should be adjusted for age and renal function and resistance to these agents by influenza A strains has been reported (160).

The antineuraminidase drugs, when used for treating influenza, reduce clinical illness and viral shedding by 2 d (161, 162). Their benefit is greatest when the respiratory illness is most severe. They prevent secondary complications of influenza, such as otitis media and sinusitis. They are effective for prophylaxis against both influenza A and B. Zanamivir is inhaled through the mouth with a specially provided applicator, and bronchospasm is possible, but unusual. Oseltamivir is given as a pill, is rapidly absorbed and achieves high blood levels, and is well tolerated but may lead to occasional nausea, which is prevented by taking the pill with food.

Comparison of the two anti-influenza drug classes shows important differences. With the antimembrane drugs (amantadine and rimantadine), resistance emerges rapidly, frequency of resistance is high, and mutant viruses are common. Neurologic

side effects are often seen with these agents. With the neuraminidase inhibitors, resistance emerges slowly, the frequency of resistance is low, and the mutant virus had reduced virulence. In addition, neurologic side effects have not been reported. It is likely that the antineuraminidase drugs will be used more widely than the older antiviral agents, and these agents have been shown to be effective not only for prophylaxis, but also for the treatment of influenza A and B, if started within 36 h after the onset of symptoms (163, 164).

SUMMARY AND RECOMMENDATIONS

The initial approach to managing patients with community-acquired pneumonia involves a determination of the presence of relevant factors that influence the likely etiologic pathogens. These factors include place of therapy (inpatient versus outpatient), the presence of cardiopulmonary disease, the presence of risk factors for drug-resistant pneumococci, the presence of risk factors for enteric gram-negative bacteria (including *P. aeruginosa*), and the severity of illness at presentation (mild, moderate, or severe). Once these assessments have been made, initial antimicrobial therapy can be selected according to the recommendations in Tables 2–5, and the choices will cover the most common pathogens likely for a given clinical setting. It is important to evaluate the response to initial therapy so that patients who are not adequately improving can be identified and properly evaluated.

The approach advocated in Tables 2–5 is different from several common clinical practices that have no firm basis in published studies. The practices include the use of sputum Gram's stain to define the likely etiologic pathogen and to guide initial therapy of community-acquired pneumonia; the use of extensive diagnostic testing in the initial evaluation of etiology; and the use of clinical syndromes to predict microbial etiology.

In several important areas of management, data are limited, and recommendations are not based on a firm scientific foundation. Future studies should focus on some of these pressing, but unanswered, questions: (*1*) How long should therapy be continued? (*2*) Should duration of therapy be related to severity of initial illness? (*3*) What role does antibiotic resistance play in the outcome of patients with CAP and how should initial therapy be modified to account for possible resistance? (*4*) Will newer diagnostic methods improve our ability to define the etiologic pathogens of community-acquired pneumonia, and will this information lead to improved outcomes? (*5*) What are the best criteria for defining the need for hospitalization? (*6*) How will antibiotic choices and guidelines for empiric therapy impact future patterns of antibiotic resistance? (*7*) Is atypical pathogen coinfection common and if so, is it prevalent all the time, or are there temporal and geographic variables to consider?

Often the distinction between pneumonia and bronchitis is uncertain, since even the chest radiograph may not be sensitive to early forms of pneumonia. This document is focused on the management of CAP, but the role of antibiotic therapy in patients with AECB needs further study, with a particular focus on whether specific types of antibiotic therapy should be targeted to specific patient populations. However, for CAP, the committee believes that guidelines can be useful for initial patient management, and the guidelines suggest therapies for illnesses that are based on the premise of using the "right drug for the right patient," recognizing that patient profiles dictate different therapies for different clinical settings.

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