

Guidelines for the Initial Management of Adults with Community-acquired Pneumonia: Diagnosis, Assessment of Severity, and Initial Antimicrobial Therapy

THIS OFFICIAL ATS STATEMENT WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1993.

Community-acquired pneumonia (CAP) remains a common and serious illness despite 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 as many as 4 million cases of community-acquired pneumonia occur annually, and as much as one fifth of these require hospitalization (1). In the outpatient setting, the mortality rate of pneumonia remains low, in the range of 1 to 5%, but among patients with community-acquired pneumonia who require hospitalization, the mortality rate approaches 25%, particularly if the patient requires admission to the intensive care unit (3-9).

In recent years, both the epidemiology and treatment of pneumonia have undergone changes. Pneumonia is increasingly common among older patients and those with comorbidity (coexisting illness). Such illnesses include chronic obstructive lung disease, diabetes mellitus, renal insufficiency, congestive heart failure, chronic liver disease, and other similar medical conditions. These patients may become infected with a variety of newly identified, or previously unrecognized, pathogens (5). At the same time, a number of new antimicrobial agents have become available, some with utility for community-acquired pneumonia. Parallel to the improvement in our antibiotic armamentarium, bacterial resistance mechanisms have evolved. In the 1990s, the prospect of pneumococcal resistance to penicillin therapy has become a reality.

This document is a summary of a conference that was convened to develop an approach to the initial management of community-acquired pneumonia, taking into account the evolving epidemiology of this infection and current therapeutic approaches. The discussion is limited to the apparently immunocompetent patient with community-acquired pneumonia because this represents the population encountered most commonly. The approach to the immunocompromised patient is different because of the large number of potential etiologic agents for pneumonia in these patients. Thus, the discussion does not deal directly with the problems of pneumonia in the HIV-infected patient or in those patients immunocompromised because 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 *initial 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. The approach emphasizes the importance of assessing severity of illness because of its relevance to decisions about hospitalization and admission to an intensive care unit. The presence of coexisting illness, as well as advanced patient age, are also important in determining the severity of illness and the patterns of clinical presentation.

Because of the nonspecificity of clinical and radiographic findings, and the limitations of diagnostic testing for identifying an etiologic pathogen, most initial therapy is necessarily *empiric*. 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. Two major variables that influence the spectrum of etiologic agents and the initial approach to therapy are: the severity of illness at initial presentation and the presence of either coexisting illness or advanced age. 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. Similarly, the presence of comorbidity or advanced age can determine the likely pathogens involved. This approach incorporates many of the same principles presented in the proceedings of a Canadian consensus conference (10). Once empiric therapy has been initiated, other questions such as the duration of therapy and the timing of the discontinuation of parenteral therapy become relevant, and these issues have been addressed. Finally, it is inevitable that empiric therapy will not be successful for all patients, and thus an approach is provided for the clinician to use if the patient is not responding to the regimen that has been selected.

ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA

Although an early etiologic diagnosis is optimal in the management of community-acquired pneumonia, the responsible pathogen is not defined in as much as 50% of patients, even when extensive diagnostic testing is performed (3-5). 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*, and respiratory viruses.

Because of the limitations of diagnostic testing, an empiric approach to initial antimicrobial therapy is usually necessary. In an attempt to develop a rational framework for such therapy, the literature addressing the incidence of specific pathogens causing community-acquired pneumonia has been reviewed. Although numerous studies detailing the incidence and etiology of pneumonia have been published, all have limitations. The approach used in this statement is based on studies that were long enough to avoid seasonal bias, recent enough to include newly recognized pathogens, and comprehensive enough to include an extensive diagnostic approach. Therefore, only prospective studies with a duration of 1 yr or more, reported in the past 10 yr, and involving adults from either Western Europe or North America were considered (3-9, 11, 12). All of these studies included an extensive diagnostic approach to define the etiologic pathogen, not relying on sputum Gram's stain and culture alone for this determination. Most of the studies 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 a small minority of the patients were receiving antimicrobials at the time of initial diagnostic evaluation.

Four patient categories were defined on the basis of information collected at the time of initial evaluation: the need for hospitalization, the severity of illness, the presence of coexisting dis-

ease, and the patient's age. The four major categories that resulted from these determinations relate not only to microbial etiology but also to ultimate prognosis and outcome. These categories are:

1. Community-acquired pneumonia occurring in patients 60 years of age or younger who have no evidence of comorbidity and who can be treated in an outpatient setting (table 1).
2. Community-acquired pneumonia occurring in patients with evidence of comorbidity and/or who are 60 yr of age or older who can be treated in an outpatient setting (table 2).
3. Community-acquired pneumonia requiring hospitalization but not admission to an intensive care unit (table 3).
4. Severe community-acquired pneumonia, generally requiring ICU care (table 4).

For each group, results from available studies were averaged to identify the most common pathogens associated with pneumonia. An attempt was made to rank the incidence of pathogens broadly, but a precise numeric incidence or percentage was not included. Nursing-home-acquired pneumonias were not categorized separately because of a lack of appropriate studies and our conclusion that the location of residence was less important than the presence of coexisting disease and age. 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*, *M. tuberculosis*, and certain viral agents (i.e., adenovirus, RSV, and influenza) (13, 14). A miscellaneous group is included in each table 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.

The most common pathogens in outpatients 60 yr of age or younger and without coexisting illness were *S. pneumoniae*, *M. pneumoniae*, respiratory viruses, *C. pneumoniae*, and *H. influenzae* (table 1). Miscellaneous pathogens included *Legionella* sp., *S. aureus*, *M. tuberculosis*, endemic fungi, and gram-negative bacilli. The mortality of patients in this category has been low (1 to 5%).

Pathogens among outpatients with coexisting disease and/or who are 60 yr of age or older include *S. pneumoniae*, respiratory viruses, *H. influenzae*, aerobic gram-negative bacilli, and *S. aureus* (table 2). Less common pathogens include *Moraxella catarrhalis*, *Legionella* sp., *Mycobacterium* sp., and endemic fungi. Mortality in this setting is also less than 5%, but about 20% of patients initially treated as outpatients may require hospitalization. Differences between the pathogens in this group and those listed in table 1 include the presence of aerobic gram-negative bacilli, *M. catarrhalis*, and *M. tuberculosis*, which were felt to be due to the presence of coexisting illness, including chronic obstructive pulmonary disease. Anaerobic infection could also be a concern in patients with comorbidity, but generally patients with this type of infection will require hospitalization (table 3).

S. pneumoniae, *H. influenzae*, polymicrobial infection (including anaerobes), aerobic gram-negative bacilli, *Legionella* sp., *S. aureus*, *C. pneumoniae*, and respiratory viruses are common among patients requiring hospitalization but who are not critically ill (table 3). Less common in this setting are *M. pneumoniae*, *M. catarrhalis*, *M. tuberculosis*, and endemic fungi. Most patients who required hospitalization were either older than 60 yr of age or had coexisting illness, and thus this group could not be subdivided in the same fashion as patients who were treated out of the hospital (3). Mortality rates reported for these patients ranged from 5 to 25%, and most of the deaths occurred within the first 7 days (3). As shown in table 3, this group differs from those with less severe pneumonia by having more patients with polymicrobial pathogens, which probably reflects coexisting processes leading

TABLE 1

OUTPATIENT PNEUMONIA WITHOUT COMORBIDITY AND 60 YEARS OF AGE OR YOUNGER*†

Organisms
<i>S. pneumoniae</i>
<i>M. pneumoniae</i>
Respiratory viruses
<i>C. pneumoniae</i>
<i>H. influenzae</i>
Miscellaneous
<i>Legionella</i> sp., <i>S. aureus</i> , <i>M. tuberculosis</i> , endemic fungi, aerobic gram-negative bacilli
Therapy
Macrolide‡
OR
Tetracycline§

* Excludes patients at risk for HIV.

† In roughly one third to one half of the cases no etiology was identified.

‡ Erythromycin. The newer macrolides, clarithromycin or azithromycin, should be considered in those intolerant of erythromycin, and in smokers (to treat *H. influenzae*).

§ 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 2

OUTPATIENT PNEUMONIA WITH COMORBIDITY AND/OR 60 YEARS OF AGE OR OLDER*†

Organisms
<i>S. pneumoniae</i>
Respiratory viruses
<i>H. influenzae</i>
Aerobic gram-negative bacilli
<i>S. aureus</i>
Miscellaneous
<i>Moraxella catarrhalis</i> , <i>Legionella</i> sp., <i>M. tuberculosis</i> , endemic fungi
Therapy
Second-generation cephalosporin
OR
TMP/SMX
OR
Beta-lactam/beta-lactamase inhibitor
±
Erythromycin or other macrolide‡

* Excludes patients at risk for HIV.

† In roughly one third to one half of the cases no etiology was identified.

‡ If infection with *Legionella* sp. is a concern.

TABLE 3

HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA*†

Organisms
<i>S. pneumoniae</i>
<i>H. influenzae</i>
Poymicrobial (including anaerobic bacteria)
Aerobic gram-negative bacilli
<i>Legionella</i> sp.
<i>S. aureus</i>
<i>C. pneumoniae</i>
Respiratory viruses
Miscellaneous
<i>M. pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>M. tuberculosis</i> , endemic fungi;
Therapy
Second- or third-generation cephalosporin‡
OR
Beta-lactam/beta-lactamase inhibitor
=
Macrolide§

* Excludes patients at risk for HIV.

† In roughly one third to one half of the cases no etiology was identified.

‡ See comments about third generation cephalosporins in text.

§ Use a macrolide if infection with *Legionella* sp. is a concern; ritampin may be added if *Legionella* sp. is documented.

TABLE 4

SEVERE HOSPITALIZED COMMUNITY-ACQUIRED PNEUMONIA*†

Organisms
<i>S. pneumoniae</i>
<i>Legionella</i> sp.
Aerobic gram-negative bacilli
<i>M. pneumoniae</i>
Respiratory viruses
Miscellaneous
<i>H. influenzae</i> , <i>M. tuberculosis</i>
Endemic fungi
Therapy
Macrolide‡
PLUS
Third-generation cephalosporin with anti- <i>Pseudomonas</i> activity§
OR
Other antipseudomonal agents such as imipenem/cilastatin, ciprofloxacin

* Excludes patients at risk for HIV.

† In roughly one third to one half of the cases no etiology was identified.

‡ Ritampin may be added if *Legionella* sp. is documented.§ Although uncommon because of high mortality associated with *P. aeruginosa* pneumonia, an aminoglycoside should be added, at least for the first few days of treatment, whether one is using a third-generation cephalosporin, imipenem, or ciprofloxacin.

to aspiration of colonized oropharyngeal secretions, and more patients with *Legionella* sp. because this infection may present with more severe disease.

Severe community-acquired pneumonia (defined below) has been separated from cases of less severe pneumonia requiring hospitalization, because of the high mortality rate of the former illness (as much as 50%) and the need for immediate recognition of the patients with this degree of illness (7-9). Although severe pneumonia was defined differently by the various investigators, a practical definition is included in a subsequent section of this statement. The pathogens most frequently identified among patients with severe pneumonia are listed in table 4. These include *S. pneumoniae*, *Legionella* sp., aerobic gram-negative bacilli, *M. pneumoniae*, respiratory tract viruses, and a group of miscellaneous pathogens (*H. influenzae*, *M. tuberculosis*, and endemic fungi).

DIAGNOSTIC STUDIES IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

A standard PA and lateral chest radiograph should be performed in patients whose symptoms and physical examination suggest

the possibility of pneumonia, although this will not be practical in all situations. This test can be useful in differentiating pneumonia from other conditions that may mimic it. In addition, the radiographic findings may suggest specific etiologies or conditions such as lung abscess, pneumonia caused by *Pneumocystis carinii*, or tuberculosis. The radiograph can also suggest coexisting conditions such as bronchial obstruction or pleural effusions. Radiography is also useful for evaluating illness severity by identifying multilobar involvement, which is an indication of severe illness (below).

Although its value is debated, some authorities feel that a properly performed Gram's stain of expectorated sputum, examined according to strict criteria, is useful in the initial evaluation of patients with pneumonia (15, 16). However, in studies of the ability of Gram's stain to predict sputum culture recovery of pneumococcus, in patients with community-acquired pneumonia, sensitivity and specificity vary widely depending on the criteria used to define a "positive" stain (15). Although sputum Gram's stain and culture are commonly used by practitioners to manage patients with community-acquired pneumonia, there are no studies correlating data from these tests to cultures of alveolar material in large numbers of patients with community-acquired pneumonia. Even if the commonly used criterion of examining and culturing a sputum sample only if it has more than 25 neutrophils and less than five squamous epithelial cells per low power field is applied, the usefulness of the data obtained is uncertain. However, direct staining of sputum may be diagnostic for some pulmonary infections, including those caused by *Mycobacterium* sp., endemic fungi, *Legionella* sp. (direct fluorescent antibody staining is required), and *P. carinii*.

Routine bacterial cultures of sputum often demonstrate pathogenic organisms, but sensitivity and specificity are poor. However, the recovery from cultures of organisms that are never part of the normal respiratory flora may be meaningful. In appropriate clinical circumstances, sputum should be cultured for *Mycobacterium* sp., *Legionella* sp., and endemic fungi. When recovery of penicillin-resistant pneumococci is anticipated (because of previous experience), sputum culture and sensitivity results can be useful. In addition, if the patient is already receiving antibiotics at the time of evaluation, sputum culture and sensitivity results may demonstrate a resistant organism. Viral cultures are not useful in the initial evaluation of patients with community-acquired pneumonia and should not be routinely performed (3).

A number of invasive diagnostic techniques to obtain lower airways specimens, uncontaminated by oropharyngeal flora, have been described (17). These include transtracheal aspiration, bronchoscopy with a protected brush catheter, bronchoalveolar lavage with or without balloon protection, and direct needle aspiration of the lung. These procedures are not indicated in most patients with community-acquired pneumonia. It may be useful to have an early accurate diagnosis in occasional patients who are severely ill. In such patients, bronchoscopy with a protected brush catheter or bronchoalveolar lavage have reasonable sensitivity and specificity when performed correctly. These procedures carry less risk and are usually more acceptable to patients and physicians than are transtracheal aspiration and direct needle aspiration of the lung, although some physicians have special expertise in using ultrathin needles for direct lung aspiration.

Hospitalized patients should have two sets of blood cultures collected, and patients with a pleural effusion should have a diagnostic thoracentesis. Pleural fluid examination should include white blood cell count and differential; measurement of protein, glucose, LDH, and pH; Gram's stain and acid-fast stain; and 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. However, acute and convalescent serologic testing may occasionally be useful for a retrospective confirmation of a suspected diagnosis, and it may be useful in epidemiologic studies. Serial complement fixing antibody titers may be useful in following patients with extensive coccidioidomycosis.

Currently available tests that directly measure specific microbial antigens are not yet useful in the initial evaluation of patients with community-acquired pneumonia. However, there is a great deal of current research in this area, and in the future, methods utilizing monoclonal antibodies, DNA probes, and polymerase chain reaction amplification may offer accurate diagnostic tests on clinical specimens.

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. However, these tests may have prognostic significance and may influence the decision to hospitalize and the choice and dose of therapy in patients with moderate to severe pneumonia. They should be obtained in patients who are hospitalized (see below), or being considered for hospitalization, and in any patient who is 60 yr of age or older or who has coexisting illness. In addition, hospitalized patients should have assessment of arterial oxygen saturation, which may also provide useful prognostic information.

The emphasis in the initial diagnostic approach is not to order extensive tests. It is quite clear that when patients have had multiple serologic tests, along with cultures of respiratory tract secretions, the yield is limited (3-5, 18). Even with extensive diagnostic testing, most investigators cannot identify the specific etiology for community-acquired pneumonia in as many as half of all patients. There is a role for some of the more advanced diagnostic tests for identification of pneumonia pathogens, but this role is primarily in epidemiologic evaluations and in the assessment of the patient whose illness is not resolving despite apparently appropriate empiric therapy (see below).

CAN CLINICAL SYMPTOMS PREDICT MICROBIAL ETIOLOGY FOR CAP?

The syndrome approach (i.e., defining the etiologic pathogen on the basis of the patient having a "typical" or "atypical" pneumonia presentation) would be the simplest, if it reliably allowed the clinician to predict specific etiologic pathogens, and thereby guide specific therapy. However, 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. 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.

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 (19, 20). Some pathogens such as *H. influenzae*, *S. aureus* and gram-negative enteric bacteria caused clinical syndromes identical to that produced by *S. pneumoniae* (21). However, other pathogens caused an atypical pneumonia syndrome that was initially attributed to *M. pneumoniae* (20), but other bacterial and viral

agents have been identified to produce a subacute illness indistinguishable from that caused by *M. pneumoniae* (22, 23). Some of these agents, however, such as *Legionella* species and influenza can cause a wide spectrum of illness, ranging from a fulminant life-threatening pneumonia to a more subacute atypical presentation (23). Thus, the term atypical pneumonia, which includes diverse entities, is often used in an unfocused manner.

The attribution of specific clinical features to an etiologic agent is a common clinical practice, particularly for patients suspected of having pneumonia with *Legionella* species (24). However, recent data have cast doubt on the specificity of these observations (4), concluding 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 using clinical criteria alone (25-28). In addition, roentgenographic evaluation does not offer significant additional diagnostic discrimination, and no pattern is sufficiently distinctive to allow classification of individual cases (29, 30).

The presence of advanced age and coexisting illness are important factors that affect the clinical presentation of pneumonia. Persons older than 65 yr of age are particularly at risk for mortality from bacteremic pneumococcal disease (31), and among the elderly, the expression of common clinical features of pneumonia is often atypical, obscured, or even absent (32).

Thus, it appears that the use of presenting clinical features, including history, physical examination, routine laboratory, and roentgenographic evaluation, does not reliably allow the clinician to make a specific etiologic diagnosis in patients with community-acquired pneumonia. Although some signs and symptoms appear to occur more commonly in *Mycoplasma* and *Legionella* pneumonia, excessive overlap with other infectious and noninfectious causes of lung infiltrates, does not permit therapeutic decisions to be made on the basis of this information.

THE DECISION TO HOSPITALIZE PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

There are no firm guidelines for when patients should be admitted to the hospital, and ultimately the decision rests with the physician after an appropriate clinical assessment. The decision to hospitalize a patient is perhaps the single most important decision during the entire course of illness with community-acquired pneumonia. There are a series of well-recognized risk factors that increase either the risk of death or the risk of a complicated course for community-acquired pneumonia (33). When these risk factors are present, especially if multiple risk factors coexist, then hospitalization should be strongly considered. The decision to hospitalize is not necessarily a commitment to long-term inpatient care. Rather, it is a decision that certain patients should be observed closely until it is clear that their infection is responding to therapy.

Specific risk factors for mortality or a complicated course of pneumonia include:

1. Age over 65 yr.
2. Presence of coexisting illnesses or other findings:
 - a. Chronic obstructive airway disease, including chronic structural disease of the lung (bronchiectasis, cystic fibrosis).
 - b. Diabetes mellitus.
 - c. Chronic renal failure.
 - d. Congestive heart failure.
 - e. Chronic liver disease of any etiology.
 - f. Previous hospitalization within 1 yr of the onset of community-acquired pneumonia.

- g. Suspicion of aspiration (gastric or oropharyngeal secretions).
 - h. Altered mental status.
 - i. Postsplenectomy state.
 - j. Chronic alcohol abuse or malnutrition.
3. Certain physical findings also predict either mortality, increased morbidity, or a complicated course (34, 35). These physical findings include:
- a. Respiratory rate in excess of 30 breaths/min.
 - b. Diastolic blood pressure \leq 60 mm Hg or a systolic blood pressure \leq 90 mm Hg.
 - c. Temperature $>$ 38.3° C (101° F).
 - d. Evidence of extrapulmonary sites of disease—presence of septic arthritis, meningitis, etc.
 - e. Confusion and/or decreased level of consciousness.
4. There are a series of laboratory findings that also predict increased morbidity or mortality. These are:
- a. White blood cell count $<$ $4 \times 10^9/L$ or $>$ $30 \times 10^9/L$ or an absolute neutrophil count below $1 \times 10^9/L$.
 - b. $P_{aO_2} <$ 60 mm Hg or P_{aCO_2} of $>$ 50 mm Hg while breathing room air.
 - c. Need for mechanical ventilation.
 - d. Evidence of abnormal renal function, as manifested by serum creatinine of $>$ 1.2 mg/dl or a blood urea nitrogen determination $>$ 20 mg/dl ($>$ 7 mmol/L) (35).
 - e. Presence of certain unfavorable chest radiographic findings, for example, more than 1 lobe involvement, presence of a cavity, rapid radiographic spreading (8) and the presence of a pleural effusion.
 - f. Hematocrit of $<$ 30% or hemoglobin $<$ 9 g/dl.
 - g. Other evidence of sepsis or organ dysfunction as manifested by a metabolic acidosis, an increased prothrombin time, an increased partial thromboplastin time, decreased platelets, or the presence of fibrin split products $>$ 1:40.

Social considerations may 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. Because community-acquired pneumonia remains a significant cause of morbidity and mortality, when the overall appearance of the patient seems unfavorable, even if the above-mentioned criteria are not fully met, it seems prudent to place the patient in the hospital on observation status for 24 to 48 h or until such time as these concerns are resolved.

DEFINITION OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA

In the last several years, several investigators (7–9, 36–38) have reported data concerning the incidence, etiology, prognostic factors, and outcome of patients with severe community-acquired pneumonia requiring intensive care. These data are important because etiologies reported in these series differ from those in the overall population with community-acquired pneumonia.

The majority of series dealing with severe community-acquired pneumonia show a distinct spectrum of etiologic agents: (1) *S. pneumoniae* and *L. pneumophila* are by far the most common organisms responsible for these pneumonias; (2) gram-negative bacilli cause pneumonia only in those patients with concomitant coexisting illness, including COPD, diabetes mellitus, and alcoholism; (3) *Pseudomonas aeruginosa* was rarely present, except in patients with bronchiectasis.

The assessment of severity of illness and mortality prediction was described in the previous section. Early recognition of pa-

tients with severe community-acquired pneumonia will aid in establishing a more focused empiric antibiotic treatment because the severity of illness appears to bear a strong relationship to the likely etiologic pathogens (table 4). Although there is not a universally accepted definition of severe community-acquired pneumonia, the presence of at least one of the following conditions justifies defining the pneumonia as severe:

1. Respiratory frequency $>$ 30 breaths/min at admission.
2. Severe respiratory failure defined by a P_{aO_2}/F_{iO_2} ratio $<$ 250 mm Hg.
3. Requirement for mechanical ventilation.
4. Chest radiograph showing bilateral involvement or involvement of multiple lobes. In addition, an increase in the size of the opacity by 50% or greater within 48 h of admission is indicative of severe pneumonia.
5. Shock (systolic blood pressure below 90 mm Hg or diastolic blood pressure below 60 mm Hg) (35).
6. Requirement for vasopressors for more than 4 h.
7. Urine output lower than 20 ml/h, or total urine output lower than 80 ml in 4 h, unless another explanation is available (39), or acute renal failure requiring dialysis.

If severe pneumonia is identified, expectant admission to the intensive care unit should be considered.

TREATMENT GUIDELINES FOR COMMUNITY-ACQUIRED PNEUMONIA

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 that was chosen is based upon a number of considerations, including the presence or absence of coexisting illness (33), severity of illness upon clinical presentation, and whether treatment is to be given on an outpatient or inpatient basis (8, 9, 35). Our current antibiotic armamentarium includes an expanding array of beta-lactams, fluoroquinolones, and macrolides, as well as the aminoglycosides, lincosamides, tetracyclines, and miscellaneous agents such as trimethoprim-sulfamethoxazole. As discussed in the section on diagnostic testing, if a specific organism is identified, then treatment with one of these agents can be specifically directed against this pathogen.

The clinician often does not face such a straightforward decision and must make an educated guess based upon the information at hand and institute therapy accordingly. Therefore, it is often the case that initial empiric therapy is by necessity somewhat broader in spectrum than is perhaps necessary. Obviously, once more information becomes available such as culture and sensitivity data appropriate modifications can be made.

Given the above-mentioned considerations, the suggested treatment regimens are presented in tables 1 to 4. When appropriate, names of classes of drugs have been used rather than specific individual agents. However, if only one drug in a given class of compounds is felt to be suitable, then the specific drug name is used; table 1 deals with outpatients who have no comorbidity and are 60 yr of age or younger, whereas table 2 deals with outpatients who have comorbidity and/or are 60 yr of age or older. In table 3 patients who are to be hospitalized but who are not severely ill are dealt with, whereas table 4 deals with patients who are hospitalized with severe community-acquired pneumonia.

Although a beta-lactam antibiotic such as penicillin is the drug of choice for infections caused by sensitive strains of *S. pneumoniae*, none of the beta-lactams provide coverage for organisms

such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. On the other hand, a macrolide such as erythromycin has excellent activity against the latter three organisms, but it is relatively inactive *in vitro* against *H. influenzae*. The new macrolides, clarithromycin and azithromycin, have *in vitro* activity against *S. pneumoniae* and *H. influenzae*, as well as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*, thereby providing the option of monotherapy when these pathogens are a consideration (40). This may be particularly appropriate for the patient 60 yr of age or younger who has no comorbidity and will be treated as an outpatient, but in whom *H. influenzae* is being considered in addition to the other usual pathogens because of a history of smoking.

Trimethoprim-sulfamethoxazole has not been formally studied in patients with pneumonia, but its *in vitro* activity and efficacy in infections other than pneumonia, against the pathogens shown in table 2, suggest that it might be an effective alternative therapy for patients who are treated according to the guidelines in this table. In addition, a carbacepham may also be useful for therapy of this type of patient. The third generation cephalosporins are listed in both tables 3 and 4, and this requires clarification. In general, these agents are less active against pneumococcus and anaerobes than are second generation cephalosporins (such as cefuroxime), but cefotaxime and ceftriaxone have been used successfully to treat community-acquired pneumonia among the types of patients listed in table 3. If *P. aeruginosa* is suspected, as would be the case for patients with structural lung disease (e.g., bronchiectasis), and with those having the clinical picture described in table 4, then the only third generation cephalosporins that can be used are ceftazidime and cefoperazone. Other alternative agents that are active against *P. aeruginosa* include imipenem/cilastatin and ciprofloxacin.

Duration of Treatment

When discussing treatment, questions arise not only as to what drugs to give, but how long to give them and when parenteral therapy can be switched to oral therapy. Surprisingly, little information exists that addresses these questions, and standard textbooks provide little, if any, specific referenced information to support statements regarding duration of treatment.

Shorter treatment courses may be possible with the introduction of a new 15-member macrolide, azithromycin. This agent has an exceedingly long half-life of 11 to 14 h compared with 1.5 to 3 and 3.8 h for erythromycin and clarithromycin, respectively. Since azithromycin has such a long half-life, it remains in the tissues longer than most agents, so that the reduced length of treatment based on the number of days of oral ingestion of the drug is somewhat misleading. At currently approved oral doses, azithromycin does not achieve high serum levels, and, consequently, this agent should not be used if bacteremic infection is suspected or if the patient is judged to be moderately or severely ill due to pneumonia. Controlled trials comparing azithromycin taken for 5 days with erythromycin and cefaclor taken for 10 days in the treatment of atypical pneumonias and acute bacterial pneumonias respectively suggest that shorter courses with this agent may be used (41, 42). However, more data are required to adequately answer this question.

The presence of coexisting illness and/or bacteremia, the severity of illness at the onset of antibiotic therapy, and the subsequent hospital course must be taken into account in determining the duration of antibiotic therapy (43). Generally, bacterial infections, such as *S. pneumoniae* pneumonia, should be treated for approximately 7 to 10 days. Cases of *M. pneumoniae* and *C. pneumoniae* may need longer therapy ranging from 10 to 14 days.

Immunocompetent patients with Legionnaire's disease should receive 14 days of treatment, whereas, immunocompromised patients may require up to 21 days of therapy.

When Can the Switch be Made from Intravenous to Oral Therapy?

The remaining question relates to when hospitalized patients receiving parenteral therapy can be switched to oral therapy. There are two perspectives from which this issue must be considered: the host and the drug. In the former case the patient must be able to take drugs by mouth and must have a functioning gastrointestinal tract. From the perspective of the drug, the key question is which antimicrobials, when given by mouth, achieve adequate tissue and serum levels. Some orally administered drugs are able to achieve serum levels comparable to parenteral therapy. These include: doxycycline, minocycline, chloramphenicol, trimethoprim-sulfamethoxazole, and most fluoroquinolones (44). For other agents, the switch to oral therapy can occur only when the higher drug levels achieved with parenteral therapy are no longer required. Thus, after a few days have elapsed and the patient has stabilized on parenteral therapy, one may not need the same degree of tissue penetration by antimicrobials, and therapy can be continued with orally administered antibiotics. Two randomized controlled studies have specifically addressed the issue of switching from intravenous to oral treatment (45, 46). The time of switch over was Day 6 and Day 3 in the two studies respectively and patients switched to oral therapy at an early time point had a good clinical response. Despite these disparate figures, a reasonable approach might be to begin oral therapy once the patient's clinical condition has stabilized and fever has subsided.

ASSESSMENT OF RESPONSE TO INITIAL ANTIMICROBIAL THERAPY

Having initiated a course of therapy based on the above guidelines, it is essential that the patient's response be carefully evaluated. With effective antimicrobial therapy, some improvement in the clinical manifestations of pneumonia should be seen in 48 to 72 h, although certain host and pathogen factors can delay resolution. Because of this natural time course of response to treatment, therapy should not be changed within the first 72 h, unless there is a marked clinical deterioration.

In patients who are otherwise healthy, fever can last for 2 to 4 days, with defervescence occurring most rapidly with *S. pneumoniae* infection, and slower with other etiologies (47). Leukocytosis usually resolves by Day 4, whereas abnormal physical findings (crackles) can persist beyond 7 days in 20 to 40% of patients. Abnormal findings on chest radiographs clear much more slowly than do clinical signs of pneumonia. For those who are younger than 50 yr of age and otherwise healthy, *S. pneumoniae* pneumonia will clear radiographically by 4 wk in only 60% of patients (48). 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 (48). *M. pneumoniae* infection can clear radiographically more rapidly than pneumococcal infection, whereas pneumonia caused by *Legionella* sp. will clear more slowly (29).

It is quite common for the radiograph to worsen initially after therapy is started, with progression of the infiltrate and/or development of a pleural effusion. If the patient has a mild pneumonia or is showing an otherwise good clinical response to treatment, 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 prog-

nostic feature, highly predictive of mortality (8). In the setting of severe pneumonia, radiographic deterioration may signify inadequately treated infection, and aggressive evaluation and initiation of broad antimicrobial therapy are necessary if there is accompanying clinical deterioration.

In general, with increasing patient age, multiple coexisting illnesses, and increasing severity of disease, the resolution of clinical signs and symptoms will be delayed. Thus, as patients are encountered who fit the descriptions in tables 1 to 4, those categorized into progressively higher numbered tables will have a more prolonged rate of pneumonia resolution.

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.

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 necessarily optimal for a pathogen such as *S. aureus*, and an aggressive search for this pathogen should be undertaken in the patient who worsens on the above regimens. 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 it 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 while the patient may appear to have community-acquired pneumonia, the etiology is an unusual organism. Such infections should be considered when clinical and radiographic findings persist, and the differential diagnosis includes tuberculosis, endemic fungal pneumonia, and *P. carinii* pneumonia. 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 (49).

A careful repeat of the history is essential in the patient who is not improving with therapy, and certain epidemiologic clues related to animal exposures and travel may indicate the presence of specific pathogens that can be detected with special serologies or cultures. 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. Travel to South East Asia can be complicated by infection with *Pseudomonas pseudomallei*, and 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 epidemiologic risk group, it should be applied.

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, and certain inflammatory lung diseases (bronchiolitis obliterans and organizing pneumonia, Wegener's granulomatosis, eosinophilic pneumonia).

Evaluation and Testing

Although there are data that indicate patients with bacteremic pneumococcal pneumonia can have a slower response to therapy than patients with nonbacteremic infection (48), there are no other clearly demonstrated relationships between the expected response to therapy and the severity of illness. However, in the setting of an inadequate response to therapy, it is appropriate to modify the extent and aggressiveness of the evaluation in direct proportion to the severity of a patient's illness.

When a patient is not adequately improving after initial empiric therapy, it is first necessary to consider the fact that the patient is already receiving antibiotics. This not only enhances the possibility that a resistant, or superinfecting, pathogen is present but it interferes with the utility of invasive diagnostic methods. Experience with bronchoscopic methods used to diagnose bacterial pneumonia has shown that when sampling is done in patients receiving antibiotics, a high false negative rate will be observed (50). However, bronchoscopy may be useful for identifying unusual organisms and drug-resistant pathogens, and the clinician should consider collecting lower respiratory tract secretions for quantitative cultures in the patient who is not responding adequately to therapy. One study has examined the utility of bronchoscopy in patients who failed empiric therapy for community-acquired pneumonia (51). Therapeutic failures were defined as early (no clinical response within 72 h) or late (initial improvement, but then after 72 hours a deterioration). The incidence of such failures was relatively low, 6.5% of 277 patients having early failure and 7% having late failure. Diagnostic bronchoscopy was done when failure occurred, and it 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.

In addition to sampling lower respiratory tract secretions, other tests should be considered. Computed tomography may reveal the presence of unsuspected collections of pleural fluid, multiple lung nodules, or cavitation within a lung infiltrate. Lung scanning and/or pulmonary angiography should be considered if the patient is at risk for pulmonary embolus with infarction. Although the routine use of serologic testing is probably not useful in the initial evaluation of patients with community-acquired pneumonia, collection of serum for serologic testing may be useful in the nonresponding patient. Serologic tests for *Legionella* sp., *Mycoplasma pneumoniae* (including cold agglutinins), viral agents, endemic fungi, and other unusual pathogens should be considered at this point. If all of the diagnostic evaluation has not been useful and if the patient is seriously ill, open lung biopsy should be considered, and should be done in an involved area of lung. This invasive approach is best for defining noninfectious processes in the immunocompetent patient, but it may also detect tuberculosis, fungal infections, and other infectious causes.

As already mentioned, it may take many weeks to months for the chest radiograph to return to normal or to stop improving. It may be useful to obtain a chest radiograph prior to discharge in all hospitalized patients and after 10 to 14 days in outpatients to

establish information on the course of resolution. Patients should be followed over the ensuing months until a new radiographic baseline is reached, and evaluation may be needed if the chest radiograph fails to return to normal, especially if the patient remains clinically ill. One series has evaluated the utility of bronchoscopy in patients with persistent radiographic and clinical abnormalities (52). In that study, bronchoscopy did yield specific diagnoses, but primarily this occurred in nonsmoking patients younger than 55 yr of age 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. In general, however, bronchoscopy is usually not needed, and patience is necessary to observe the full course of radiographic clearing of community-acquired pneumonia.

Complications of Pneumonia

In addition to the diagnoses considered above, the patient who remains ill despite empiric therapy may have extrapulmonary complications of pneumonia. These include metastatic infection, which can occur in as many as 10% of patients with bacteremic pneumococcal pneumonia (53). Metastatic infections include meningitis, arthritis, endocarditis, pericarditis, peritonitis, and empyema, and these complications should be considered. Particularly because of concern about empyema, any patient with an inadequate clinical response to therapy should have a repeat chest radiograph and any pleural fluid should be sampled, cultured, and analyzed for cell count and chemistry. In addition to metastatic infection, other 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 sepsis syndrome from pneumonia, the chest radiograph and clinical course may deteriorate because of the presence of the adult respiratory distress syndrome and multiple system organ failure.

SUMMARY AND RECOMMENDATIONS

An initial approach to managing patients with community-acquired pneumonia involves a determination of three factors. (1) Should the patient be treated in the hospital or as an outpatient? (2) Does the patient with pneumonia have a serious coexisting illness or advanced age (> 60 yr)? (3) How severely ill is the patient at the time of initial evaluation? Once these assessments have been made, initial antimicrobial therapy can be selected according to the recommendations in tables 1 to 4, 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 these tables is different from several common clinical practices that have no firm basis in published studies. These include: the use of sputum Gram's stain to define the likely etiologic pathogen and to guide initial therapy of community-acquired pneumonia; the routine use of extensive diagnostic testing in the initial evaluation of etiology; 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) When is it safe to switch hospitalized patients from parenteral therapy to oral therapy? (4) Will newer diagnostic methods

improve our ability to define the etiologic pathogens of community-acquired pneumonia? (5) What pathogens are responsible for pneumonia when no organism is identified, even with extensive diagnostic testing?

This Statement was prepared by an ad hoc Committee of the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections. Members of the Committee were:

MICHAEL S. NIEDERMAN, M.D. (*Chairman*)
 JOHN B. BASS JR., M.D.
 G. DOUGLAS CAMPBELL, M.D.
 ALAN M. FEIN, M.D.
 RONALD F. GROSSMAN, M.D.
 LIONEL A. MANDELL, M.D.
 THOMAS J. MARRIE, M.D.
 GEORGE A. SAROSI, M.D.
 ANTONIO TORRES, M.D.
 VICTOR L. YU, M.D.

References

- Garibaldi RA. Epidemiology of community-acquired respiratory tract infections in adults: incidence, etiology, and impact. *Am J Med* 1985; 78:32S-7S.
- U.S. Department of Commerce, Bureau of the Census. *Statistical Abstract of the United States*. 104th ed. Washington DC: USGPO, 1984.
- Bates JH, Campbell GD, Barron AL, McCracken GA, Morgan PN, Moses EB, Davis CM. Microbial etiology of acute pneumonia in hospitalized patients. *Chest* 1992; 101:1005-12.
- Fang GD, Fine M, Orloff J, Arisumi D, Yu VL, Kapoor W, Grayston JT, Wang SP, Kohler R, Muder RR, Yee YC, Rihs JD, Vickers RM. New and emerging etiologies for community-acquired pneumonia with implication for therapy: a prospective multicenter study of 359 cases. *Medicine (Baltimore)* 1990; 69:307-16.
- Marrie TJ, Durant H, Yates L. Community-acquired pneumonia requiring hospitalization: a 5 year prospective study. *Rev Infect Dis* 1989; 11:586-99.
- Woodhead MA, MacFarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987; 1:671-4.
- Ortqvist A, Sterner G, Nilsson JA. Severe community-acquired pneumonia: factors influencing need of intensive care treatment and prognosis. *Scand J Infect Dis* 1985; 17:377-86.
- Torres A, Serra-Batlles J, Ferrer A, Jimenez P, Celis R, Cobo E, Rodriguez-Roisin R. Severe community-acquired pneumonia: epidemiology and prognostic factors. *Am Rev Respir Dis* 1991; 144:312-8.
- Pachon J, Prados MD, Capote F, Cuello JA, Gamacho J, Verano A. Severe community-acquired pneumonia: etiology, prognosis, and treatment. *Am Rev Respir Dis* 1990; 142:369-73.
- Mandell LA, Niederman MS. The Canadian Community Acquired Pneumonia Consensus Group. Antimicrobial treatment of community acquired pneumonia in adults: a conference report. *Can J Infect Dis* 1993; 4:25-8.
- Erard PH, Moser F, Wenger A, Saghafi L, Bille J, Francioli P, and a group of practitioners at Neuchatel. Prospective study on community-acquired pneumonia diagnosed and followed up by private practitioners. Abstract of the 1991 Interscience Conference on Antimicrobial Agents and Chemotherapy. Abstract no. 56; 108.
- British Thoracic Society Research Committee and the Public Health Laboratory Service. The aetiology, management and outcome of severe community-acquired pneumonia in the intensive care unit. *Respir Med* 1992; 86:7-13.
- Stead WW, Lofgren JP, Warren E, Thomas C. Tuberculosis as an epidemic and nosocomial infection among the elderly in nursing homes. *N Engl J Med* 1985; 312:1483-7.
- Gross PA, Rodstein M, La Montagne JR, Kaslow RA, Saath AJ, Wallenstein S, Neufeld R, Denning C, Gaerlan P, Quinnan GV. Epidemiology of acute respiratory illness during an influenza outbreak in a nursing home: a prospective study. *Arch Intern Med* 1988; 148:559-61.
- Rein MF, Gwaltney JM Jr, O'Brien WM, Jennings RH, Mandell GL. Accuracy of Gram's stain in identifying pneumococci in sputum. *JAMA* 1978; 239:2671-3.
- Boerner DF, Zwadyk P. The value of the sputum Gram's stain in community-acquired pneumonia. *JAMA* 1982; 247:642-5.
- Middleton RM, Kirkpatrick MB, Bass JB Jr. Invasive techniques for the diagnosis of lower respiratory tract infections. In: Niederman MS, Sarosi G, Glassroth J, eds. *Respiratory Infections: A Scientific Basis for Management*. Philadelphia: W. B. Saunders, (In Press).
- Woodhead MA, Arrowsmith J, Chamberlain-Webber R, Wooding S, Wil-

- liams I. The value of routine microbial investigation in community-acquired pneumonia. *Respir Med* 1991; 85:313-7.
19. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia. *JAMA* 1938; 11:2377-84.
 20. Chanock RM, Hayflick L, Barile MF. Growth on artificial medium of an agent associated with atypical pneumonia and its identification as a PPLO. *Proc Natl Acad Sci USA* 1961; 47:8-11.
 21. Levin DC, Schwartz MI, Matthay RA, LaForce FM. Bacteremic *Hemophilus influenzae* pneumonia in adults: a report of 24 cases and a review of the literature. *Am J Med* 1977; 62:219-24.
 22. Grayston JT, Kuo CC, Wang SP, Altman J. A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. *N Engl J Med* 1986; 315:161-8.
 23. Kirby BD, Snyder K, Meyer R, Finegold SM. Legionnaires' disease: report of 65 nosocomially acquired cases and a review of the literature. *Medicine (Baltimore)* 1980; 59:188-205.
 24. Nguyen MLT, Yu VL. *Legionella* infection. *Clin Chest Med* 1991; 12:257-68.
 25. Isaccs D. Problems in determining the etiology of community-acquired childhood pneumonia. *J Pediatr Infect Dis* 1989; 8:145-8.
 26. Woodhead MA, MacFarlane JT. Comparative clinical laboratory features on *Legionella* with pneumococcal and *Mycoplasma* pneumonias. *Br J Dis Chest* 1987; 81:133-9.
 27. Farr BM, Kaiser DL, Harrison BDW, Connolly CK. Prediction of microbial aetiology at admission to hospital for pneumonia from the presenting clinical features. *Thorax* 1989; 44:1031-5.
 28. Chan CHS, Cohen M, Pang J. A prospective study of community-acquired pneumonia in Hong Kong. *Chest* 1992; 101:442-6.
 29. MacFarlane JT, Miller AC, Smith WHR, Morris AH, Rose DH. Comparative radiographic features of community-acquired Legionnaires' disease, pneumococcal pneumonia, *Mycoplasma* pneumonia, and psittacosis. *Thorax* 1984; 39:28-33.
 30. Tew J, Calenoff L, Berlin BS. Bacterial or nonbacterial pneumonia: accuracy of radiographic diagnosis. *Radiology* 1977; 124:607-12.
 31. Finkelstein MS, Petkun WM, Freedman ML, Antopol SC. Pneumococcal bacteremia in adults: age-dependent differences in presentation and in outcome. *J Am Geriatr Soc* 1983; 31:19-27.
 32. Venkatesan P, Gladman J, MacFarlane JT, Barer D, Berman P, Kinnear W, Finch RG. A hospital study of community-acquired pneumonia in the elderly. *Thorax* 1990; 45:254-8.
 33. Fine MJ, Smith DN, Singer DE. Hospitalization decision in patients with community-acquired pneumonia: a prospective cohort study. *Am J Med* 1990; 89:713-21.
 34. Council of the British Thoracic Society. The hospital management of community-acquired pneumonia. *J R Coll Physicians Lond* 1987; 21:267-9.
 35. Farr BM, Stoman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. *Ann Intern Med* 1991; 115:428-36.
 36. Woodhead MA, MacFarlane JT, Rodgers FG, Laverick A, Pilkington R, Macrae AD. Aetiology and outcome of severe community-acquired pneumonia. *J Infect* 1985; 10:204-10.
 37. Sorensen J, Cederholm I, Carlsson C. Pneumonia: a deadly disease despite intensive care treatment. *Scand J Infect Dis* 1986; 18:329-35.
 38. Feldman C, Kallenbach JM, Levy H, Reinach SG, Hurwitz MD, Thorburn JR, Koornhof HJ. Community-acquired pneumonia of diverse aetiology: prognosis features in patients admitted to an intensive care unit and a "severity of illness." *Intensive Care Med* 1989; 15:302-7.
 39. Celis R, Torres A, Gatell JM, Almela M, Rodriguez-Roisin R, Agusti-Vidal A. Nosocomial pneumonia: a multivariate analysis of risk and prognosis. *Chest* 1988; 93:318-24.
 40. Hardy DJ, Swanson RN, Rode RA, Marsh K, Shipkowitz NL, Clement JJ. Enhancement of the *in vitro* and *in vivo* activities of clarithromycin against *Hemophilus influenzae* by 14-hydroxy-clarithromycin, its major metabolite in humans. *Antimicrob Agents Chemother* 1990; 34:1407-13.
 41. Schonwald S, Gunjaca M, Kolacny-Babic L, Car V, Gosev M. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonias. *J Antimicrob Chemother* 1990; 25(Suppl A):123-6.
 42. Kinasewitz G, Wood RG. Azithromycin versus cefaclor in the treatment of acute bacterial pneumonia. *Eur J Clin Microbiol Infect Dis* 1991; 10:872-7.
 43. McGehee JL, Podnos SD, Pierce AK, Weissler JC. Treatment of pneumonia in patients at risk of infection with gram-negative bacilli. *Am J Med* 1988; 84:597-602.
 44. Cunha BA. Antibiotic pharmacokinetic considerations in pulmonary infections. *Semin Respir Infect* 1991; 6:168-82.
 45. Khan FA, Basir R. Sequential intravenous-oral administration of ciprofloxacin vs ceftazidime in serious bacterial respiratory tract infections. *Chest* 1989; 96:528-37.
 46. Paladino JA, Sperry HE, Backes JM, Gelber JA, Serianne DJ, Cumbo TJ. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. *Am J Med* 1991; 91:462-70.
 47. Lehtomaki K. Clinical diagnosis of pneumococcal, adenoviral, mycoplasmal and mixed pneumonias in young men. *Eur Respir J* 1988; 1:324-9.
 48. Jay SJ, Johanson WG, Pierce AK. The radiographic resolution of *Streptococcus pneumoniae* pneumonia. *N Engl J Med* 1975; 293:798-801.
 49. Rodrigues J, Niederman MS, Fein AM, Pai PB. Nonresolving pneumonia in steroid-treated patients with obstructive lung disease. *Am J Med* 1992; 93:29-34.
 50. Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. *Chest* 1992; 102(Suppl:557S-64S).
 51. Orqvist A, Kalin M, Lejdebom L, Lundberg B. Diagnostic fiberoptic bronchoscopy and protected brush culture in patients with community-acquired pneumonia. *Chest* 1990; 97:576-82.
 52. Feinsilver SH, Fein AM, Niederman MS, Schuitz DE, Faegenburg DH. Utility of fiberoptic bronchoscopy in nonresolving pneumonia. *Chest* 1990; 98:1322-6.
 53. Marrie TJ. Bacteremic pneumococcal pneumonia: a continuously evolving disease. *J Infect* 1992; 24:247-55.