REVIEW ARTICLE

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Community-Acquired Pneumonia

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Long recognized as a major cause of death, pneumonia has been studied intensively since the late 1800s, the results of which led to many formative insights in modern microbiology.[1,2] Despite this research and the development of antimicrobial agents, pneumonia remains a major cause of complications and death. Community-acquired pneumonia (CAP) is a syndrome in which acute infection of the lungs develops in persons who have not been hospitalized recently and have not had regular exposure to the health care system.

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CAUSE

In the preantibiotic era, *Streptococcus pneumoniae* caused 95% of cases of pneumonia.[1] Although pneumococcus remains the most commonly identified cause of CAP, the frequency with which it is implicated has declined,[3] and it is now detected in only about 10 to 15% of inpatient cases in the United States.[4-7] Recognized factors contributing to this decline include the widespread use of pneumococcal polysaccharide vaccine in adults,[8] the nearly universal administration of pneumococcal conjugate vaccine in children,[9] and decreased rates of cigarette smoking.[10,11] In Europe and other parts of the world where pneumococcal vaccines have been used less often and smoking rates remain high, pneumococcus remains responsible for a higher proportion of cases of CAP.[12,13]

Other bacteria that cause CAP include *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and other gram-negative bacilli (Table 1). Patients with chronic obstructive pulmonary disease (COPD) are at increased risk for CAP caused by *H. influenzae* and *Mor. catarrhalis*.[14] *P. aeruginosa* and other gram-negative bacilli also cause CAP in persons who have COPD or bronchiectasis, especially in those taking glucocorticoids.[15] There is a wide variation in the reported incidence of CAP caused by *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (so-called atypical bacterial causes of CAP), depending in part on the diagnostic techniques that are used.[16,17] Newly available polymerase-chain-reaction (PCR) techniques should help to clarify this point. Another type of bacterial pneumonia caused by legionella species occurs in certain geographic locations and tends to follow specific exposures. Mixed microaerophilic and anaerobic bacteria (so-called oral flora) are often seen on Gram's staining of sputum, and these organisms may be responsible for cases in which no cause is found.

During influenza outbreaks, the circulating influenza virus becomes the principal cause of CAP that is serious enough to require hospitalization, with secondary bacterial infection as a major contributor.[18-20] Respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, coronavirus, and rhinovirus are commonly detected in patients with CAP, but it may be unclear to what extent some of these organisms are causing the disease or have predisposed the patient to secondary infection by bacterial pathogens.[16,21-23] Other viruses that cause CAP include the Middle East respiratory syndrome coronavirus (MERS-CoV), which recently emerged in the Arabian Peninsula, and avian-origin influenza A (H7N9), which

Table 1. Infectious and Noninfectious Causes of a Syndrome Consistent with Community-Acquired Pneumonia (CAP) Leading to Hospital Admission.*

Common Causes	Less Common Causes	Uncommon Causes
Infectious		
Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, influenza virus, other respiratory viruses†	*Pseudomonas aeruginosa* or other gram-negative rods, *Pneumocystis jirovecii, Moraxella catarrhalis,* mixed microaerophilic and anaerobic oral flora	*Mycobacterium tuberculosis,* nontuberculous mycobacteria, nocardia species, legionella species, *Mycoplasma pneumoniae,*‡ *Chlamydophila pneumoniae,*‡ *Chlamydophila psittaci, Coxiella burnetii, Histoplasma capsulatum,* coccidioides species, *Blastomyces dermatitidis,* cryptococcus and aspergillus species
Noninfectious		
Pulmonary edema, lung cancer, acute respiratory distress syndrome	Pulmonary infarction	Cryptogenic organizing pneumonia, eosinophilic pneumonia, acute interstitial pneumonia, sarcoidosis, vasculitis (granulomatosis with polyangiitis), pulmonary alveolar proteinosis, drug toxicity, radiation pneumonitis

* Causes of pneumonia vary according to the patient population, host immune status, and geographic region. No cause is determined in about half of patients with CAP despite intense investigation. Normal flora, especially streptococci from the upper airways, may be responsible for many of these cases.

† Routine use of the polymerase-chain-reaction (PCR) assay has substantially increased the detection of these agents, which include parainfluenza virus, respiratory syncytial virus, adenovirus, coronavirus, human metapneumovirus, and rhinovirus.

‡ The frequency of this organism in causing CAP is uncertain because serologic techniques have been unreliable. Currently available PCR assays may provide reliable information in the future.

recently emerged in China; both of these newly identified viruses have since spread elsewhere.[24,25]

Nontuberculous mycobacteria and, in endemic areas, fungi such as histoplasma and coccidioides species cause subacute infections that are characterized by cough, fever, and new pulmonary infiltrates. *Coxiella burnetii* may cause acute pneumonia with cough, high fever, severe headache, and elevated aminotransferase levels. One cannot overemphasize the breadth of potential causes, infectious and noninfectious, of a syndrome consistent with CAP (Table 1). Most studies of the cause of CAP have been performed at tertiary care hospitals, which may not be representative of the population at large, although similar pathogens have been reported in studies of outpatients.[26,27] Despite the most conscientious efforts to determine the cause, no cause is found in about half the patients who are hospitalized for CAP in the United States, indicating an important area for future investigation.[5,22,26]

APPROACH TO DIAGNOSIS

The diagnosis of CAP is more challenging than it might appear to be. The typical teaching is that pneumonia is characterized by a newly recognized lung infiltrate on chest imaging together with fever, cough, sputum production, shortness of breath, physical findings of consolidation, and leukocytosis.[14] Confusion and pleuritic chest pain are often present. However, some patients with pneumonia (especially those who are elderly) do not cough, produce sputum, or have an elevated white-cell count, and about 30% (including a greater proportion of elderly patients) are afebrile at admission.[3,5,28-30] New lung infiltrates may be difficult to identify in patients with chronic lung disease, in obese patients, and in those for whom only portable chest radiography is available, or they may be present but are due to noninfectious causes. In one study, 17% of patients who were hospitalized for CAP did not have an infection; pulmonary edema, lung cancer, and other miscellaneous causes were responsible (Table 1).[5] Although practitioners need to consider the diverse causes of a pneumonia-like syndrome before empirically prescribing antimicrobial therapy, such conservatism must be balanced by the recognition that, for patients with CAP who are ill enough to require hospitalization, early initiation of antimicrobial therapy increases the likelihood of a good outcome.[14]

TECHNIQUES TO DETERMINE CAUSE

In patients requiring hospitalization, clinicians should make a conscientious effort to determine the causative organism. Such an effort enables the physician to direct treatment toward a specific pathogen and facilitates a rational approach to changing therapy if a patient does not have a re-

sponse to empirical treatment or has an adverse drug reaction. Pathogen-directed therapy greatly fosters antibiotic stewardship, decreasing the cost of care and reducing the risk of complications such as *Clostridium difficile* infection. In hospitalized patients with CAP, we favor obtaining Gram's staining and culture of sputum, blood cultures, testing for legionella and pneumococcal urinary antigens, and multiplex PCR assays for *Myc. pneumoniae*, *Chl. pneumoniae*, and respiratory viruses, as well as other testing as indicated in patients with specific risk factors or exposures. A low serum procalcitonin concentration (<0.1 μg per liter) can help to support a decision to withhold or discontinue antibiotics.[31]

Microscopic examination of pulmonary secretions may provide immediate information about possible causative organisms. Results on Gram's staining and culture of sputum are positive in more than 80% of cases of pneumococcal pneumonia when a good-quality specimen (>10 inflammatory cells per epithelial cell) can be obtained before, or within 6 to 12 hours after, the initiation of antibiotics. The yield diminishes with increasing time after antibiotics have been initiated and with decreasing quality of the sputum sample.[32] Nebulization with hypertonic saline (so-called induced sputum) may increase the likelihood of obtaining a valid sample.

Blood cultures are positive in about 20 to 25% of inpatients with pneumococcal pneumonia[33] but in fewer cases of pneumonia caused by *H. influenzae* or *P. aeruginosa* and only rarely in cases caused by *Mor. catarrhalis*. In hematogenous *Staph. aureus* pneumonia, blood cultures are nearly always positive, but they are positive in only about 25% of cases in which inhalation or aspiration is responsible for the CAP.[34]

Newer diagnostic techniques have become important in establishing the cause of CAP. Enzyme-linked immunosorbent assay (ELISA) of urine samples detected pneumococcal cell-wall polysaccharide in 77 to 88% of patients with bacteremic pneumococcal pneumonia[35-37] and in 64% with nonbacteremic pneumonia.[35] The more sensitive multiplex-capture assay for pneumococcal capsular polysaccharides is not yet available for clinical use in the United States but should increase the yield.[12] ELISA for legionella urinary antigen is positive in about 74% of patients with pneumonia caused by *Legionella pneumophila* serotype 1,[38] with increased sensitivity in more severe disease.[39] Performing sputum culture with the use of selective media is necessary to detect other legionella species.

PCR is a remarkably sensitive and specific technique for identifying respiratory pathogens, especially viruses. Commercially available PCR assays can detect most important respiratory viruses as well as *Myc. pneumoniae* and *Chl. pneumoniae*.[40] For influenza, PCR is far more sensitive than rapid antigen tests and has become the standard for diagnosis.[41] On the basis of PCR, a respiratory virus is identified in 20 to 40% of adults hospitalized for CAP.[5,16,22,42] However, the interpretation of a positive test may be difficult, since respiratory viruses may either cause pneumonia directly or predispose the patient to bacterial pneumonia.[5,22,43] Thus, positive results on PCR do not exclude the possibility that bacterial pneumonia is present. Nearly 20% of patients with CAP who have proven bacterial pneumonia are coinfected with a virus.[5,22,43]

PCR detection of bacteria in respiratory samples is also problematic. In most instances, bacteria that cause pneumonia reach the lungs after colonizing the upper airways, so a positive PCR result may reflect colonization or infection.[44] In one study in Africa, quantitative PCR of nasopharyngeal swabs obtained from patients with CAP, most of whom had the acquired immunodeficiency syndrome (AIDS), was positive in 82% of patients who had pneumococcal pneumonia, with few false positive results.[45] The generalizability of this method to patients without AIDS in developed countries remains to be determined.

TREATMENT

SCORING OF DISEASE SEVERITY

Scoring systems may predict the severity of disease and help determine whether a patient with CAP requires hospitalization or admission to an intensive care unit (ICU).[46,47] Validated instruments include the Pneumonia Severity Index (PSI) (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org),[48] the CURB-65 score (a measure of confusion, blood urea nitrogen, respiratory rate, and blood pressure in a patient ≥65 years of age),[49] and the guidelines of the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS).[14,50] The decision to hospitalize a patient ultimately depends on the physician's

judgment, but all factors that are contained in these scoring systems should be considered. Because the PSI is so age-dependent, an elevated score in a young adult should be regarded with alarm.

The SMART-COP score (evaluating systolic blood pressure, multilobar infiltrates, albumin, respiratory rate, tachycardia, confusion, oxygen, and pH), which was designed to predict which patients require ICU admission, was originally reported to be 92% sensitive, as compared with 74% for the PSI and 39% for CURB-65.[51] We have recently found that the PSI is more sensitive than SMART-COP and much more sensitive than CURB-65 for determining which patients will need ICU admission.[52]

GUIDELINES FOR EMPIRICAL THERAPY

Guidelines for empirical antimicrobial therapy for CAP have contributed to a greater uniformity of treatment,[14,53,54] and their use in hospitalized patients has been associated with better outcomes.[55,56] Once the diagnosis of CAP is made, antimicrobial therapy should be started as soon as possible and at the site where the diagnosis is made.[14] An initial target period of 4 hours from initial contact with the medical care system until antibiotic administration was later changed to 6 hours, in part because the data on which the target period was based were regarded as low quality[55] and because the use of a target period resulted in overdiagnosis of CAP and inappropriate use of antimicrobial agents.[57,58] In 2012, the target period was retired altogether and replaced by the recommendation that treatment be initiated promptly and at the point of care where the diagnosis of pneumonia was first made.

Outpatients with CAP are generally treated empirically. A cause of infection is usually not sought because of the substantial cost of diagnostic testing. For outpatients without coexisting illnesses or recent use of antimicrobial agents, IDSA/ATS guidelines recommend the administration of a macrolide (provided that <25% of pneumococci in the community have high-level macrolide resistance) or doxycycline. For outpatients with coexisting illnesses or recent use of antimicrobial agents, the guidelines recommend the use of levofloxacin or moxifloxacin alone or a beta-lactam (e.g., amoxicillin–clavulanate) plus a macrolide.

By contrast, guidelines from the United Kingdom and Sweden recommend amoxicillin or penicillin as empirical therapy for CAP in outpatients.[53,54] Several factors favor the use of a beta-lactam as empirical therapy for CAP in outpatients. First, most clinicians do not know the level of pneumococcal resistance in their communities, and *Str. pneumoniae* is more susceptible to penicillins than to macrolides or doxycycline. Second, even though the prevalence of *Str. pneumoniae* as a cause of CAP has decreased, it seems inappropriate to treat a patient with a macrolide or doxycycline to which 15 to 30% of strains of *Str. pneumoniae* are resistant.[59] In some parts of the world, rates of pneumococcal resistance to macrolides are far higher.[60] Third, if a patient does not have a prompt response to a beta-lactam, a macrolide or doxycycline can be substituted to treat a possible atypical bacterial infection, such as that caused by *Myc. pneumoniae.* In the United States, because one third of *H. influenzae* isolates and a majority of *Mor. catarrhalis* isolates produce beta-lactamase, amoxicillin–clavulanate may be preferable to amoxicillin or penicillin, especially in patients with underlying lung disease.

For patients with CAP who require hospitalization and in whom no cause of infection is immediately apparent, IDSA/ATS guidelines recommend empirical therapy with either a beta-lactam plus a macrolide or a quinolone alone.[14] These regimens have been studied extensively and generally produce a cure in about 90% of patients with CAP of mild or moderate severity.[48,61,62]

For patients requiring ICU admission, the guidelines recommend a minimum of a beta-lactam plus either a macrolide or a quinolone.[14] Three scenarios merit special mention. First, when influenza is active in the community, patients with CAP should be treated with oseltamivir even if more than 48 hours have elapsed since the onset of symptoms.[63,64] If the likelihood of influenza infection is high, treatment should be continued even if the relatively insensitive rapid antigen detection test is negative; a negative result on PCR for influenza virus probably allows for the discontinuation of anti-influenza therapy.[65] Because of the high rate of bacterial superinfection, ceftriaxone and vancomycin or linezolid (for methicillin-resistant *Staph. aureus* [MRSA]) should also be given unless a good-quality respiratory specimen shows no bacteria on Gram's staining and there is no other evidence of bacterial infection. Droplet and contact precautions should be

used when influenza is suspected. Second, in patients at high risk for *Staph. aureus* pneumonia (e.g., those taking glucocorticoids or those with influenza), vancomycin or linezolid should be added to treat MRSA. Ceftaroline, which is active against *Staph. aureus*, including MRSA, as well as *Str. pneumoniae* and *H. influenzae*, may eventually replace ceftriaxone plus vancomycin or linezolid as anti-MRSA regimen, although it has not yet been approved by the Food and Drug Administration for treating MRSA pneumonia. Third, when *P. aeruginosa* is a consideration, as in patients with structural lung disease such as COPD or bronchiectasis (especially if they are receiving treatment with glucocorticoids or other immunosuppressive drugs), an antipseudomonal beta-lactam or carbapenem should be given. IDSA/ATS guidelines recommend the use of two antipseudomonal drugs because it is difficult to predict the susceptibility pattern of pseudomonas species. Initial therapy may be empirical, but antibiotics should be tailored to the causative organism, which underlines the clear advantage of establishing the cause of infection.

EMPIRICAL THERAPY — DOES ONE SIZE FIT ALL?

The IDSA/ATS guidelines were written in an attempt to develop a uniform set of recommendations that would provide appropriate antimicrobial therapy for the majority of patients with CAP. Although individual causative organisms cannot be determined with certainty on the basis of findings at presentation, the medical literature supports the concept that constellations of clinical findings may guide diagnosis and selection of therapy (Table 2).[66-70] Our approach to the selection of an appropriate antimicrobial regimen is intended to balance the tension between a failure to treat, on the one hand, and overtreatment by attempting to cover all possible causes, on the other.

A patient whose constellation of findings includes an acute onset of chills and fever, cough with sputum production, pleuritic chest pain, a high or suppressed white-cell count with increased band forms, a dense segmental or lobar consolidation, or a serum procalcitonin level of more than 0.25 μg per liter is likely to have typical bacterial pneumonia, such as pneumococcal pneumonia.[5,66-70] Such patients should be hospitalized (if indicated on the basis of the PSI) and treated with a beta-lactam (e.g., ceftriaxone or ampicillin–sulbactam) plus a macrolide or with a quinolone (levofloxacin or moxifloxacin).[5,66-70] If risk factors raise concern for *P. aeruginosa* infection, we use an antipseudomonal beta-lactam (e.g., cefepime or piperacillin–tazobactam). In contrast to the IDSA/ATS guidelines (which recommend the use of two antipseudomonal agents), we typically give a second antipseudomonal agent only to patients who are severely ill (Table 3). In patients who have a milder version of this syndrome and who do not require hospital admission, amoxicillin–clavulanate may be given in place of a parenteral beta-lactam. A quinolone should be used judiciously and only in outpatients who have substantial coexisting illnesses or who have recently taken antibiotics from another class. In contrast

Table 2. Clinical Features Associated with Specific Causes of CAP.

Favoring typical bacterial or legionella pneumonia
Hyperacute presentation
Presentation with septic shock
Absence of upper respiratory symptoms
Initial upper respiratory illness followed by acute deterioration (suggesting viral infection with bacterial superinfection)
White-cell count, >15,000 or ≤6000 cells per cubic millimeter with increased band forms
Dense segmental or lobar consolidation
Procalcitonin level, ≥0.25 μg per liter
Favoring atypical bacterial (mycoplasma or chlamydophila) pneumonia
Absence of factors that favor typical bacterial pneumonia
Family cluster
Cough persisting >5 days without acute deterioration
Absence of sputum production
Normal or minimally elevated white-cell count
Procalcitonin level, ≤0.1 μg per liter
Favoring nonbacterial (viral) pneumonia
Absence of factors that favor bacterial pneumonia
Exposure to sick contacts
Upper respiratory symptoms at time of presentation
Patchy pulmonary infiltrates
Normal or minimally elevated white-cell count
Procalcitonin level, ≤0.1 μg per liter
Favoring influenza pneumonia
Absence of factors that favor typical bacterial pneumonia
Influenza active in the community
Sudden onset of flulike syndrome
Positive diagnostic test for influenza virus

Table 3. Empirical Treatment of CAP.

Outpatient*
For syndromes suggesting typical bacterial pneumonia: amoxicillin–clavulanate with the addition of azithromycin if legionella species are a consideration; levofloxacin or moxifloxacin may be used instead
For syndromes suggesting influenza pneumonia: oseltamivir with observation for secondary bacterial infection
For syndromes suggesting viral pneumonia other than influenza: symptomatic therapy
For syndromes suggesting mycoplasma or chlamydophila pneumonia: azithromycin or doxycycline
Inpatient†
For initial empirical therapy: a beta-lactam (ceftriaxone, cefotaxime, or ceftaroline) plus azithromycin; levofloxacin or moxifloxacin may be used instead
If influenza is likely: oseltamivir‡
If influenza is complicated by secondary bacterial pneumonia: ceftriaxone or cefotaxime plus either vancomycin or linezolid§ in addition to oseltamivir
If *Staphylococcus aureus* is likely: vancomycin or linezolid in addition to the antibacterial regimen
If pseudomonas pneumonia is likely: antipseudomonal beta-lactam (piperacillin–tazobactam, cefepime, meropenem, or imipenem–cilastatin)¶ plus azithromycin

* The decision to treat pneumonia on an outpatient basis should be made after assessing the need for hospitalization and only if follow-up contact is planned. The use of quinolones is typically reserved for outpatients with substantial coexisting illnesses or recent use of antibiotics from another class.

† Patients who are hospitalized for pneumonia are sufficiently likely to have a bacterial infection that antibacterial agents are nearly always prescribed unless an alternative diagnosis is strongly suspected. In every hospitalized patient, all reasonable efforts should be made to determine the causative organism, and antimicrobial therapy should be directed toward identified organisms.

‡ In patients who are severely ill, intravenous zanamivir can be obtained after approval of an emergency investigational new drug application.

§ These regimens target the most likely causes of bacterial pneumonia secondary to influenza pneumonia, including *Streptococcus pneumoniae, Haemophilus influenzae, Str. pyogenes,* and *Staph. aureus*. Ceftaroline may be effective against these bacterial pathogens, including methicillin-resistant *Staph. aureus* (MRSA), but it is not yet approved by the Food and Drug Administration for MRSA pneumonia.

¶ A second antipseudomonal drug (ciprofloxacin or an aminoglycoside) can be added in patients with severe CAP in whom *P. aeruginosa* is likely, because susceptibility is difficult to predict. Therapy can be narrowed to one agent with activity against gram-negative bacilli once susceptibility results are available.

to the IDSA/ATS guidelines, because of concern about pneumococcal resistance, we would not use doxycycline or azithromycin alone to treat outpatients in whom the syndrome suggests typical bacterial infection.

Patients with CAP who have none of the factors that favor bacterial infection and who have known exposure to sick contacts, upper respiratory symptoms at the time of presentation, patchy pulmonary infiltrates, a normal or minimally elevated white-cell count with a normal differential, and a procalcitonin level of 0.1 μg per liter or less are unlikely to have bacterial pneumonia (Table 2). It might be best to treat their symptoms and observe them. If they have been started on antibacterial agents for typical bacterial pneumonia, these drugs could be discontinued, especially if initial studies for bacteria are negative.[5,31] If influenza is active in the community and the syndrome is consistent (e.g., sudden onset, fever, cough, and myalgias), oseltamivir should be given unless the result on PCR is negative for influenza. Documentation of a noninfluenza respiratory virus by means of PCR in such patients supports the choice of observation alone without antibiotics. *Myc. pneumoniae* infection is more likely in young adults who have low-grade fever and a nonproductive cough for 5 or more days without acute deterioration, especially if the illness developed in a family cluster.[68,70,71] Treatment for *Myc. pneumoniae* infection with a macrolide seems appropriate, particularly if testing for viruses is negative.

When patients are hospitalized for CAP and no causative organism is identified, most clinicians presume that a bacterial infection is responsible and treat with full courses of broad-spectrum antibacterial therapy.[72] Some studies suggest that the use of biomarkers can distinguish bacterial from nonbacterial pneumonia.[31,73] In a meta-analysis of 14 randomized trials, procalcitonin guidance for antibiotic use was associated with a reduction in antibiotic use without an increase in either mortality or treatment failure.[73] Because of the substantial overlap in procalcitonin levels among individual patients, such testing should be only one of several factors considered in the decision to withhold antibiotics.[5]

DURATION OF THERAPY

Early in the antibiotic era, pneumonia was treated for about 5 days; some studies even showed that a single dose of penicillin G procaine was curative.[74,75] The standard duration of treatment later evolved to 5 to 7 days.[76,77] A meta-analysis of studies comparing treatment durations of 7 days or less with durations of 8 days or more showed no differences in outcomes,[78] and prospective studies have shown that 5 days of therapy are as effective as 10 days[79] and 3 days are as effective as 8.[80] Nevertheless, practitioners have gradually increased the duration of treatment for CAP to 10 to 14 days.[72,81] A responsible approach to balancing antibiotic stewardship with concern about insufficient antibiotic therapy would be to limit treat-

ment to 5 to 7 days, especially in outpatients, or in inpatients who have a prompt response to therapy.[14,77,82]

Pneumonia that is caused by *Staph. aureus* or gram-negative bacilli tends to be destructive, and concern that small abscesses may be present has led clinicians to use more prolonged therapy, depending on the presence or absence of coexisting illnesses and the response to therapy. Hematogenous *Staph. aureus* pneumonia mandates treatment for at least 4 weeks, but segmental or lobar pneumonia that is caused by this organism may be treated for 2 weeks.[83] Cavitating pneumonia and lung abscesses are usually treated for several weeks; some experts continue treatment until cavities have resolved. The lack of a response to seemingly appropriate treatment in a patient with CAP should lead to a complete reappraisal, rather than simply to selection of alternative antibiotics (Table 4).

Table 4. Reasons for a Lack of Response to Treatment of CAP.

Correct organism but inappropriate antibiotic choice or dose
Resistance of organism to selected antibiotic
Wrong dose (e.g., in a patient who is morbidly obese or has fluid overload)
Antibiotics not administered
Correct organism and correct antibiotic but infection is loculated (e.g., most commonly empyema)
Obstruction (e.g., lung cancer, foreign body)
Incorrect identification of causative organism
No identification of causative organism and empirical therapy directed toward wrong organism
Noninfectious cause
Drug-induced fever
Presence of an unrecognized, concurrent infection

IMMUNOMODULATORY DRUGS

Macrolides inhibit important intracellular signaling pathways and suppress production of transcription factors, such as nuclear factor κB and activator protein 1, which, in turn, decrease the production of inflammatory cytokines and the expression of adhesion molecules.[84] Many, but not all, retrospective studies have shown that the addition of a macrolide to a beta-lactam antibiotic to treat pneumococcal pneumonia or all-cause CAP reduces morbidity and mortality, presumably by inhibiting the inflammatory response.[85,86]

Statins block the synthesis of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, inhibiting the synthesis of farnesyl pyrophosphate and geranylgeranyl pyrophosphate (which are needed to activate G proteins), thereby dampening inflammatory responses.[87] Observational studies have shown better outcomes in patients who were taking statins at the time of admission for pneumonia, even though such patients tend to have a greater number of coexisting illnesses related to coronary artery disease.[86] No data from randomized trials to examine these effects of macrolides or statins in patients with CAP are available. The potential benefit of macrolides must be balanced against the very small increase in sudden cardiac deaths observed in patients taking azithromycin.[88] Other studies, however, have shown conflicting results.[89,90] A randomized trial of adjunctive simvastatin in patients with ventilator-associated pneumonia was stopped early because no 28-day mortality benefit was seen in those who received this drug.[91]

NONINFECTIOUS COMPLICATIONS

Influenza pneumonia[92,93] and bacterial pneumonia[94-97] are each strongly associated with acute cardiac events. In a veterans hospital, myocardial infarction and new major arrhythmias (most commonly, atrial fibrillation) were each seen in 7 to 10% of patients who were admitted for CAP, worsening of heart failure occurred in nearly 20%, and one or more of these complications occurred in 25% of patients.[94,97] It is likely that myocardial infarction occurs when pulmonary inflammation releases cytokines that up-regulate inflammation in a vulnerable atherosclerotic plaque.[96,98] The mechanism for atrial fibrillation is uncertain; this arrhythmia usually resolves spontaneously within a few weeks. Heart failure probably reflects added stress on the heart together with decreased oxygenation. These cardiac events are associated with substantial increases in mortality.[99]

OUTCOMES

The 30-day rate of death in patients who are hospitalized for CAP is approximately 10 to 12% (Tables S1 and S2 in the Supplementary Appendix).[48,61,62] After discharge from the hospital, about 18% of patients are readmitted within 30 days.[100] Many patients, especially elderly ones,

may take several months to return to their previous state of health, and some never do.[101,102] In those who survive for 30 days, mortality is substantially increased at 1 year and, in the case of pneumococcal pneumonia, remains elevated for 3 to 5 years,[103,104] suggesting that development of CAP serves as a marker for underlying conditions that limit lifespan.

FUTURE DIRECTIONS

Important unresolved problems remain with respect to CAP. Despite the most diligent efforts, no causative organism is identified in half of patients. It is unclear what proportion of these cases are attributable to infection by so-called typical or atypical bacterial pathogens, oral flora, viruses, or other pathogens. The increased use of PCR will elucidate the frequency with which legionella, chlamydophila, and mycoplasma species, along with other pathogens, cause CAP. It remains to be determined whether the availability of sensitive diagnostic tests such as PCR will increase the use of targeted therapies and reduce dependence on empirical antibiotic therapy. Increasing antibiotic resistance in bacteria may compound the difficulty of selecting an effective regimen. Randomized trials are needed to determine whether the antiinflammatory activity of macrolides or statins is beneficial in treating CAP.

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