Community-acquired pneumonia (CAP) is a common disorder that is potentially life-threatening, especially in older adults and patients with comorbid disease. Despite substantial progress in therapeutic options, CAP remains a primary cause of death from infectious disease in the United States. The mainstay of treatment for most patients is appropriate antimicrobial therapy. This article reviews the principles for initial antimicrobial therapy, highlights some of the differences in approaches to antimicrobial drug selection in selected guidelines, and includes new recommendations for empiric and pathogen-directed therapy of CAP.

Principles of antimicrobial therapy

As an acute infection, pneumonia may be caused by a wide variety of pathogens. The major goals of therapy, along with support of oxygenation and other vital functions in severe cases, are eradication of the infecting organism and resultant resolution of clinical disease.

Until more accurate and rapid diagnostic methods are developed, the initial antimicrobial treatment for most patients is empirical. Recommendations for such therapy in this article apply to most of the cases encountered by clinicians; however, pneumonia can encompass many different diseases, and clinicians need to consider specific risk factors for each patient. These factors include aspiration risks, pneumonia occurring during a community epidemic, and pneumonia complicating possible or probable influenza.
Epidemiologic association with specific pathogens always must be considered (eg, *Coccidioidomyces* spp in the southwestern United States, severe acute respiratory syndrome [SARS] in travelers from parts of Asia).

Although some authorities propose a syndromic approach to therapy (counting on the predictability of a cause based on the presenting clinical manifestations), most data indicate that the presenting clinical features are not specific enough to reliably predict the cause of CAP [1–3]. Some studies have shown that atypical pathogens (such as *Chlamydophila pneumoniae*, *Legionella* spp, viruses) may serve as co-pathogens with traditional bacteria, making it difficult to know when it is appropriate to treat only a bacterial pathogen [4–6].

The selection of specific antimicrobial regimens for empiric therapy is based largely on a number of principles, including the prediction of the most likely pathogens (aided by knowledge of commonly encountered pathogens in a geographic area and an appreciation of their usual susceptibilities patterns); and the presence of medical comorbidities that may influence the pathogen, increase likelihood for drug-resistant *Streptococcus pneumoniae* (DRSP), and potentially be a risk factor for clinical failure (Box 1). Other factors for consideration of specific antimicrobials include spectrum of activity, potential for inducing resistance, pharmacokinetics and pharmacodynamics, efficacy, safety profile, clinical trials showing proven efficacy, and cost.

*Likely pathogens of community-acquired pneumonia*

Although CAP may be caused by many possible pathogens, a limited number of common pathogens are responsible for most cases. The emergence of newly recognized pathogens, such as the novel coronavirus associated with SARS, continually increases the challenge for appropriate management of CAP.

### Box 1. Principles of empiric antimicrobial therapy for community-acquired pneumonia

The most likely pathogens (including most common pathogens and pathogens of epidemiologic consideration)

Local antimicrobial-susceptibility patterns

Potential for inducing antimicrobial resistance

Risk factors for drug-resistant *S pneumoniae* (especially recent antimicrobial drug use)

Medical comorbidities

Pharmacokinetic and pharmacodynamic considerations

Safety profile

Cost efficacy

Clinical trials showing proven efficacy
Table 1 lists the most common pathogens associated with CAP based on the collective results of recent studies and based on the severity of illness as judged by the site of care (outpatient versus inpatient) [7]. Collectively, *S pneumoniae* is the most frequently isolated pathogen. Relative to other pathogens, *Mycoplasma pneumoniae, C pneumoniae, Haemophilus influenzae, Legionella pneumophila*, and respiratory viruses are also common. The atypical pathogens (with the exception of *L pneumophila*) are not identified often in clinical practice, however, because there is not a specific, rapid, or standardized test for their detection. Although influenza remains the most predominant viral cause of CAP in adults, other recognized pathogens include respiratory syncytial virus; parainfluenza virus; and less commonly, adenovirus, metapneumovirus, herpesvirus, varicella, SARS-associated coronavirus, and measles. In a study of nonimmunocompromised adults who were admitted for CAP, 18% of patients had evidence of a viral cause, and in 9% of patients, a respiratory virus was the only pathogen identified [8].

*Staphylococcus aureus, Enterobacteriaceae, and Pseudomonas aeruginosa* pathogens are found in a selected group of patients who have had influenza, previously have taken antimicrobial drugs, or have pulmonary comorbidities. [9] Identified risk factors for gram-negative bacteria include recent antibiotic therapy, pulmonary comorbidity, and recent hospitalization; the latter two risk factors also predict *P aeruginosa* as a likely gram-negative pathogen [9].

Pneumonia caused by community-associated methicillin-resistant *S aureus* (CA-MRSA) has been observed [10,11]. This type of pneumonia is uncommon, but it is important to recognize because of its potentially serious consequences. CA-MRSA strains seem to be distinct from hospital-acquired strains from epidemiologic, genotypic, and phenotypic perspectives [12]. They tend to be less resistant to antimicrobial drugs than are hospital-acquired MRSA strains and almost always contain a novel-type IV staphylococcal cassette chromosome (SCCmec) gene. Many of these strains have been found to contain the gene for Panton-Valentine leukocidin, which

| Cause of community-acquired pneumonia according to severity/site of care | Ambulatory patients | Hospitalized (non-ICU) patients | Patients with severe (ICU) pneumonia |
|---|---|---|---|
| *S pneumoniae* | *S pneumoniae* | *S pneumoniae* |
| *M pneumoniae* | *M pneumoniae* | *Legionella spp* |
| *H influenzae* | *C pneumoniae* | *H influenzae* |
| *C pneumoniae* | *Legionella spp* | Gram-negative bacilli |
| Respiratory viruses<sup>a</sup> | Aspiration | *S aureus* |

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

*Data from File TM Jr. Community-acquired pneumonia. Lancet 2003;362:1991–2001.*
is responsible for a toxin that is associated with the clinical features of necrotizing pneumonia, shock, and respiratory failure, and the formation of abscess and empyema. Most of the cases published to date have been in children; however, the authors observed this strain in adults during the winter season of 2003 to 2004, and many cases were associated with preceding influenza.

The frequency of other causes (eg, *Mycobacterium tuberculosis*, *Chlamydia psittaci* [psittacosis], *Coxiella burnetii* [Q fever], *Francisella tularensis* [tularemia], melioidosis, endemic fungi [histoplasmosis, coccidioidomycosis, blastomycosis]) vary with the epidemiologic setting (Table 2).

In patients admitted to the ICU with severe CAP, the predominant pathogens are pneumococcus, atypical pathogens, *H influenzae*, enteric gram-negative bacteria, and *S aureus* [13]. A carefully done bronchoscopic study of nursing-home patients with severe CAP in the setting of suspected aspiration identified enteric gram-negative bacteria as the predominant pathogens and found that anaerobes were uncommon, often were identified with other bacteria, and did not require specific therapy [14]. The atypical pathogens responsible for severe CAP may vary over time, accounting collectively for approximately 20% of pneumonia episodes, but the dominant pathogen from a pathogenic aspect is *Legionella* spp [15].

Although objective confirmation is often difficult, multiple organisms that infect a patient concurrently or sequentially may cause CAP [4,5]. Influenza A or *C pneumoniae* infection might be followed by a secondary infection with *S pneumoniae*. In one study of patients hospitalized with serologically diagnosed *C pneumoniae* pneumonia, 45% of patients were infected with other pathogens, the most common of which was the pneumococcus [6]. The importance of treating multiple infecting organisms has not been established; however, identification of one pathogen should not preclude evaluation for other causes, particularly when the case of CAP is not responding to therapy.

**Drug-resistant Streptococcus pneumoniae**

The emergence of resistant respiratory pathogens, particularly strains of DRSP, has influenced initial empirical management of CAP. The clinical relevance of DRSP for pneumonia is imprecise and has been the subject of several reviews [16–18]. Few well-controlled studies examine the impact of in vitro resistance on clinical outcomes of CAP. Published studies are limited by small sample sizes, biases inherent in observational design, and the relative infrequency of isolates showing high-level resistance among clinical isolates. Most studies suggest that current levels of β-lactam resistance generally do not result in treatment failures in patients with CAP when appropriate agents (ie, amoxicillin, ceftriaxone, cefotaxime) and doses are used. The available data suggest that the clinically relevant level of penicillin resistance is a minimal inhibitory concentration (MIC) of at least 4 mg/L.
| Condition                                                                 | Commonly encountered pathogens                                                                 |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Alcoholism                                                                | *S. pneumoniae*, oral anaerobes                                                                 |
| Chronic obstructive pulmonary disease and/or smoking                      | *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, * Legionella* spp, *Chlamydia pneumoniae*   |
| Poor dental hygiene                                                       | Oral anaerobes                                                                                    |
| Aspiration/Lung abscess                                                  | Oral anaerobes                                                                                    |
| Exposure to bats or soil enriched with bird droppings                     | Histoplasma capsulatum                                                                           |
| Exposure to birds                                                         | *Chlamydia psittaci*, avian influenza (poultry exposure)                                          |
| Exposure to rabbits                                                       | *Francisella tularensis*                                                                         |
| Exposure to farm animals or parturient cats                              | *Coxiella burnetti* (Q fever)                                                                    |
| HIV infection (early)                                                     | *S. pneumoniae*, *H. influenzae*, *M. tuberculosis*                                              |
| HIV infection (late)                                                      | Above plus *J. carinii*, *Cryptococcus*, *Histoplasma*                                           |
| Travel to or residence of southwestern United States                      | *Coccidioides* spp                                                                               |
| Travel to or residence of Asia                                           | *Burkholderia pseudomallei*, severe acute respiratory disease                                     |
| Influenza active in community                                             | *Influenza*, *S. pneumoniae*, *S. aureus*, *H. influenzae*                                       |
| Structural lung disease (eg, bronchiectasis)                             | *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *S. aureus*                                   |
| Injection drug use                                                        | *S. aureus*, *S. anserobes*, *M. tuberculosis*, *S. pneumoniae*                                  |
| Endobronchial obstruction                                                 | Anaerobes, *S. pneumoniae*, *H. influenzae*, *S. aureus*                                        |
| Recent hospitalization, nursing home residence                           | *DRSP*, gram-negative bacilli, *S. aureus*                                                      |
| In context of bioterrorism                                                | *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *F. tularensis* (Tularemia)          |
| Guideline                          | Outpatient<sup>a</sup>                                                                 | General ward<sup>a</sup>                                                                 | ICU/Severe<sup>a</sup>                                                                 |
|-----------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| **North American Guidelines**     | If no significant risks for **DRSP<sup>b</sup>**: macrolide<sup>c</sup> or doxycycline | **β-Lactam** (ceftriaxone, cefotaxime, ampicillin/sulbactam) plus macrolide<sup>c</sup> | **β-Lactam** (ceftriaxone, cefotaxime, ampicillin/sulbactam, piperacillin/tazobactam) plus macrolide<sup>c</sup> or fluoroquinolone<sup>d</sup> (if β-lactam allergy, use fluoroquinolone<sup>d</sup> plus clindamycin) |
|                                   | If risks for **DRSP<sup>b</sup>**: antipneumococcal fluoroquinolone<sup>d</sup> or high-dose amoxicillin (3 g/d) or amoxicillin/clavulanate plus macrolide (if amoxicillin is used and there is a concern for *H. influenzae*, use agent active for β-lactamase producing strains<sup>c</sup>) |                                                                                         | Modifying factors of structural lung disease: antipseudomonal agent (piperacillin/tazobactam, carbapenem, or cefepime) plus antipseudomonal fluoroquinolone (high-dose ciprofloxacin or levofloxacin) |
|                                   | **β-Lactam** (ceftriaxone, cefotaxime, ampicillin/sulbactam) plus macrolide<sup>c</sup> | (Specified as severe pneumonia)                                                          | Not specified                                                                            |
|                                   | (can use doxycycline if macrolide not tolerated) or antipneumococcal fluoroquinolone<sup>d</sup> alone |                                                                                         |                                                                                          |
| **Japanese Respiratory Society [36]** | (Specified as mild or moderate pneumonia)                                                | (Specified as severe pneumonia)                                                          |                                                                                          |
|                                   | When bacterial pneumonia is suspected: a penicillin-type drug (with a β-lactamase inhibitor) orally or penicillin-type drug (injection) or cephap-type drug | For younger patients without underlying illness: injection use or fluoroquinolone          | Consider as for inpatients, elderly patients, or patients with underlying illness          |
| British Thoracic Society [35] | Amoxicillin 500–1000 mg three times a day (alternative: erythromycin or clarithromycin) |
|--------------------------------|-------------------------------------------------------------------------------------|

When atypical pneumonia is suspected: macrolide or tetracycline

For elderly or underlying illness:
- Carbapenem plus tetracycline or macrolide or third-generation cephem plus clindamycin plus tetracycline or macrolide

If admitted for nonclinical reasons or previously untreated in the community: amoxicillin (alternative: macrolide)

If admitted for pneumonia and oral therapy appropriate:
- Amoxicillin plus erythromycin or clarithromycin (alternative: antipneumococcal fluoroquinolone)

If parenteral appropriate: ampicillin or benzylpenicillin plus erythromycin or clarithromycin (alternative: intravenous levofloxacin)

Co-amoxiclav or 2nd/3rd gene ceph plus [iv erythro or clarithro, +/- rifampin] (fluoroquinolone with enhanced pneumococcal activity plus benzylpenicillin as alternative)

Second- or third-generation cephem plus intravenous erythromycin or clarithromycin, with or without rifampin

**Abbreviations:** ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America.

- a Site of care.
- b β-Lactam therapy within the past 3 months, hospitalization within the past month, alcoholism, immune-suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, exposure to a child in a day care center.
- c If chronic obstructive pulmonary disease, use a macrolide active against β-lactamase–producing *H. influenzae* (ie, azithromycin, clarithromycin).
- d Gatifloxacin, levofloxacin, moxifloxacin.
One report suggests that if cefuroxime is used to treat pneumococcal bacteremia and if the organism is resistant in vitro, the outcome may be worse than if other therapies are used. Other discordant therapies did not impact mortality [19]. Data suggest that resistance to macrolides and respiratory fluoroquinolones (levofloxacin) may result in clinical failure; however, interpretation is limited by the relatively small number of patients reported [20–22,23–25].

Risk factors for penicillin-resistant *S pneumoniae* have been identified: age <2 years or >65 years, β-lactam therapy within the previous 3 months, alcoholism, medical comorbidities, immunosuppressive illness or therapy, and exposure to a child in a day care center [16,19,26]. Although the relative predictive value of these risk factors is unclear, treatment with antimicrobial drugs is likely to be the most significant factor. Several sets of data have shown that recent therapy with β-lactams, macrolides or quinolones is a risk factor for pneumococcal resistance to the same class of antibiotic, and repeated courses of the same antibiotic class are a risk factor for pneumococcal resistance to that agent [27–30]. One study has found that in the presence of pneumococcal bacteremia, use of a β-lactam or macrolide within the past 6 months increased the likelihood of infection with a penicillin-resistant organism [30]. In that study, recent use of a quinolone did not predict an increased likelihood of penicillin resistance, but other studies have shown that repeated use of quinolones does predict an increased risk for quinolone-resistant pneumococci [25,29]. It remains uncertain if this risk applies equally to all quinolones or if it is more of a concern for less active pneumococcal agents (levofloxacin) than for more active agents (moxifloxacin, gemifloxacin) [23–25].

**Different approaches to empiric antimicrobial drug selection**

Numerous guidelines for recommended antimicrobial management of CAP have been published. Specific recommendations for empirical therapy for CAP as included in several published guidelines from North America, the United Kingdom, and Japan are listed in Table 3 [31–36]. A combined consensus guideline from the American Thoracic Society (ATS) and Infectious Diseases Society of America is being prepared (M. Niederman and T. File, personal communication, 2004).

**Recommendations for empirical therapy of outpatients**

North American (NA) guidelines variably recommend macrolides, doxycycline, an antipneumococcal fluoroquinolone (eg, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin), or the combination of a β-lactam plus macrolide as treatment options for patients who are mildly ill and can be treated as outpatients [31–34]. In general, the NA guidelines recommend a macrolide as first-line treatment for outpatients with no comorbidity or
risk factors for DRSP. The rationale is that macrolides provide effective therapy for the most common bacterial pathogens in such patients (ie, primarily *S. pneumoniae*) and the atypical organisms, especially *M. pneumoniae* and *C. pneumoniae*, which are common in outpatients. The positioning of the macrolides as prominent first-line agents in the NA guidelines partially is based on the presumption that the new macrolides (azithromycin, clarithromycin) can be effective against MRSP strains, in which lower-level resistance results from increased drug efflux and resulting MICs that often are less than 8 µg/mL. Because data indicate that *mef*-mediated resistance is becoming associated with higher MICs (from a median of 4 µg/mL to a median of 8 µg/mL), it is reasonable to consider an alternative therapy (ie, respiratory fluoroquinolone, ketolide, or high-dose amoxicillin [≥3 g/d for adults] plus a macrolide) if risk factors for DRSP are present.

In contrast, the primary agents recommended in the British Thoracic Society (BTS) guidelines are β-lactams, primarily penicillins, rather than macrolides [35]. The rationale is that these agents are effective against *S. pneumoniae* and, when given in high doses, are even effective for most strains with decreased sensitivity to penicillin. Because most of the macrolide resistance in Europe is *erm*-mediated, high-level resistance, the macrolides are not regarded as optimal first-line empirical agents to treat this pathogen if *S. pneumoniae* infection is considered likely. The British guidelines place less significance in the need to treat empirically patients who are infected with atypical pathogens and are ambulatory (mild disease). The guidelines suggest that because *M. pneumoniae* exhibits epidemic periodicity every 4 to 5 years and largely affects younger patients, a policy for initial empirical therapy that aims always to cover this pathogen is unnecessary.

The two approaches represented by the NA and BTS guidelines differ primarily because of the greater emphasis in North America to routinely treat the atypical pathogens and the fact that MRSP in Europe is of higher-level resistance than in North America. More studies are needed to answer the question regarding the need to routinely treat atypical pathogens. The Japanese guidelines advocate initial therapy based on a syndromic approach (ie, macrolides or tetracycline treatment for likely atypical pneumonia and penicillin-type therapy for bacterial pneumonia) [36].

**Recommendations for empirical therapy of inpatients**

The NA guidelines recommend treatment with a β-lactam plus a macrolide or monotherapy with a fluoroquinolone for patients who are admitted to the general ward. This rationale partly results from studies showing that these regimens are associated with a significant reduction in the mortality rate, compared with the mortality rate associated with cephalosporin treatment alone [37–40]. Although limited by their retrospective design, these studies have found that the use of macrolides as part of an initial combination therapy (usually with a cephalosporin agent) or
fluoroquinolone monotherapy in patients who require hospitalization seems to be associated with decreased mortality rates or shorter hospital stays, compared with the use of a cephalosporin alone [37–40]. The specific cause of infection was not determined in these studies; however, the added coverage for atypical pathogens partly may explain this observation. The recommendations in the BTS guidelines are similar to in the NA guidelines. The Japanese guidelines stratify patients based on age and presence of underlying illness, and use of an “injection use fluoroquinolone” is recommended for younger patients with less serious disease. A combination regimen is recommended for other patients.

For patients with severe CAP who require ICU admission, all of the guidelines recommend comprehensive antimicrobial therapy to cover infection with \textit{S pneumoniae} (including DRSP), \textit{Legionella} spp, and potentially gram-negative bacilli, including \textit{Pseudomonas} spp in selected-cases.

**Updated recommendations for empirical antimicrobial therapy**

The authors’ recommendations for empiric therapy of CAP in outpatients, patients admitted to a general ward, and patients requiring ICU admission are listed in Box 2. These therapeutic regimens are considered to be effective for most patients (ie, patients who are likely to have one of the more common causes, which are listed in Table 1). The authors recognize that a significant minority of patients has epidemiologic risk factors for which other pathogens, and other antimicrobial therapy is warranted in such patients. Such epidemiologic factors and associated pathogens are listed in Table 2.

**Outpatients**

For patients who have mild (ambulatory) pneumonia, do not have significant medical comorbidities (ie, diabetes, chronic inflammatory lung disease, liver or renal insufficiency, malignancy, congestive heart failure), and have not been recently treated with antimicrobial agents, treatment with an extended-spectrum macrolide (clarithromycin, azithromycin) or doxycycline is appropriate.

In recent studies, the most common pathogens in such patients were \textit{S pneumoniae}, \textit{M pneumoniae}, \textit{C pneumoniae}, and \textit{H influenzae} [41,42]. \textit{Mycoplasma} spp most commonly were found in patients younger than 50 years and without significant comorbid conditions or abnormality of vital signs. \textit{S pneumoniae} was the most common pathogen in older patients and patients with significant underlying disease. \textit{H influenzae} was found in 5% of patients and mostly in patients with comorbidities, such as cigarette smoking. The importance of therapy for \textit{Mycoplasma} spp and \textit{Chlamydia} spp infection in mild CAP has been the subject of some conjecture, because
many infections are self-limiting. Studies from the 1960s indicate that treatment of mild \textit{M pneumoniae} CAP reduces the morbidity of pneumonia and shortens the duration of symptoms [43].

The macrolides constitute a long-standing class of antimicrobials in the treatment of outpatients with CAP in the United States. This class includes the erythromycin-type agents (including dirithromycin), the extended-spectrum macrolide and clarithromycin and the azalide azithromycin. These agents have had a significant role in the management of CAP because of their activity against \textit{S pneumoniae} and the atypical pathogens. Although erythromycin is the least expensive drug, it is not used as often because of gastrointestinal intolerance and lack of activity against \textit{H influenzae}. In light of this activity against \textit{H influenzae}, an advanced macrolide-and-azalide combination should be used when considering treatment for outpatients with comorbidities such as chronic obstructive pulmonary disease.

Numerous randomized clinical trials document the efficacy of the advanced macrolide-and-azalide combination as monotherapy (azithromycin, clarithromycin) for outpatients [44–50]. Despite the reports of clinical failures of macrolides in the treatment of outpatients with pneumococcal pneumonia, the numbers are relatively small in light of the large number of patients treated. When such patients were hospitalized and treated with a \beta-lactam and a macrolide, they generally survived [21,22,51]. Most of these patients had risk factors for which monotherapy with a macrolide is not recommended in the guidelines. For patients without significant risks for DRSP or gram-negative bacilli, monotherapy with a macrolide still can be considered appropriate. Doxycycline is included as a cost-effective alternative, in part based on in vitro data, which indicate that the drug is at least as effective as erythromycin for treating pneumococcal isolates; however, little clinical trial data are available [52].

Fluoroquinolone treatment of ambulatory CAP without comorbid conditions or recent antimicrobial use is discouraged for fear that widespread use may lead to the development of fluoroquinolone resistance among respiratory pathogens and to the colonization of other pathogens. Studies of outpatients have shown that many quinolone recipients could receive other agents as preferred first-line therapy, that some quinolone recipients may not require antibiotic treatment, and that the doses and durations employed are often incorrect. This type of usage pattern has raised concerns about promoting the rapid development of antibiotic resistance to the quinolone class of antibiotics [52].

The likelihood for the development of DRSP and enteric gram-negative bacteria is increased in patients with comorbidities or recent antimicrobial therapy. For such patients, recommended empiric therapeutic options include a respiratory fluoroquinolone (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin), a ketolide alone (ie, telithromycin) if enteric gram-negative bacteria are not a concern, or combination therapy with a \beta-lactam plus a macrolide (with doxycycline as alternative) is effective for
Box 2. Empirical selection of antimicrobial agents for treating patients with community-acquired pneumonia

Outpatients
A. Previously healthy and no use of antimicrobial drugs within the previous 3 months:
   An extended-spectrum macrolide (clarithromycin or azithromycin) or doxycycline
B. Presence of comorbidities (ie, diabetes, liver disease, renal insufficiency, malignancy, chronic inflammatory lung disease, congestive heart disease) or use of antimicrobial drugs within the previous 3 months (depending on the class of antibiotics recently given, an alternative option from a different class should be selected):
   A respiratory fluoroquinolone (gatifloxacin, levofloxacin, moxifloxacin, gemifloxacin)
   Telithromycin if no risks for enteric gram-negative organisms
   A β-lactam (high-dose amoxicillin [eg, 1 g three times daily; or 2 g of amoxicillin/clav 2 twice daily is preferred].
   Alternatives: cefpodoxime, cefuroxime, cefprozil, and cefdinir) plus a macrolide (alternative: doxycycline)
   Ceftriaxone (intramuscular or intravenous) plus macrolide, or doxycycline

Inpatients in the general ward
Respiratory FQ or β-lactam (preferred agents include cefotaxime, ceftriaxone, ampicillin/sulbactam; consider ertapenem in selected patients) plus macrolide or doxycycline
For carefully selected patients with no risk factors for DRSP or gram-negative organisms, the use of monotherapy with azithromycin can be considered
Consider risk factors for other pathogens (see Table 1).

Inpatients in the ICU
Pseudomonas not a consideration
A β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, ertapenem) plus azithromycin or a respiratory FQ. For patients with penicillin allergy, a respiratory fluoroquinolone, with or without clindamycin
Pseudomonas is a consideration (severe structural lung diseases, such as bronchiectasis, chronic obstructive pulmonary disease with repeated antimicrobial or steroid use)
An antipneumococcal, antipseudomonal β-lactam (piperacillin, cefepime, imipenem, meropenem) plus ciprofloxacin or levofloxacin (750 mg)
An antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and an intravenous macrolide or intravenous antipneumococcal quinolone
For patients with penicillin allergy, aztreonam plus levofloxacin (750 mg); or aztreonam plus moxifloxacin or gatifloxacin, with or without aminoglycoside
Consider risk factors for other pathogens (see Table 1).

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*S pneumoniae* infection. These regimens may be appropriate for use in patients who are without comorbidities or recent antimicrobial and who live in places where there is a high prevalence of *S pneumoniae* infection with high-level macrolide resistance. Based on pharmacodynamic principles, high-dosage amoxicillin (1 g of amoxicillin three times daily or 2 g of amoxicillin and potassium clavulanate two times daily) should be effective for more than 93% of cases of *S pneumoniae* infection, and amoxicillin is the preferred β-lactam [53]. For patients without type I penicillin allergy [53], a selected cephalosporin (cefpodoxime, cefuroxime) can be used as an alternative, but these drugs are less active in vitro than is high-dose amoxicillin.

Telithromycin is the first ketolide approved for the treatment of mild-to-moderate CAP and is useful when DRSP is a risk. This agent has shown efficacy in some patients with bacteremia and with higher pneumonia severity of illness (PSI) scores [54,55]. In vitro, telithromycin is active against *S pneumoniae* which is resistant to other antimicrobials, including penicillin, macrolides, and fluoroquinolones. Data from several controlled, double-blind CAP trials suggest that telithromycin is as effective as the comparators, including amoxicillin, clarithromycin, and trovafloxacin [56–58]. Available information suggests that telithromycin, which is only available as an oral agent, will have an important role in the treatment of CAP caused *S pneumoniae* or the common atypical pathogens. The efficacy of this agent in *H influenzae* infection is similar to that of the new macrolides, but more data involving patients with such infection are needed.

Another possible option for empiric treatment of outpatients with modifying factors, depending on the setting, is the use of parenteral intramuscular or intravenous ceftriaxone that is given with an oral macrolide, ketolide, or doxycycline. Outpatient services are increasingly available, and
Parenteral antimicrobial therapy may be appropriate for selected patients with mild disease [59].

**Inpatients in the general ward**

Recommended regimens for inpatients in the general ward are a β-lactam plus a macrolide (alternatively, doxycycline or ketolide) or monotherapy with a fluoroquinolone that is considered effective for treating *S. pneumoniae* infection. Numerous studies have shown that empiric treatment with either of these regimens is associated with a significant reduction in mortality rate and length of hospital stay, compared with treatment with cephalosporin alone [38–40]. The preferred β-lactams are effective in treating *S. pneumoniae* infection and are not overly broad spectrum; however, treatment with other antipneumococcal, antipseudomonal agents (eg, cefepime, piperacillin, tazobactam) can be appropriate when more resistant pathogens are involved in the pneumonia or coexisting infections. In January 2002, the National Committee for Clinical Laboratory Standards (NCCLS) increased the MIC breakpoints for cefotaxime and ceftriaxone treatment of nonmeningeal *S. pneumoniae* infections. These new breakpoints acknowledge that nonmeningeal infections caused by strains that formerly were considered to be intermittently susceptible, and even some strains that were regarded as resistant, can be treated successfully with the usual doses of these β-lactams. Ertapenem is included as a β-lactam option in light of two randomized, double-blind studies showing that such treatment has equivalent results compared with the results of ceftriaxone therapy [60,61]. This drug also has excellent activity for anaerobic organisms and most Enterobacteriaceae (including producers of extended-spectrum β-lactamase producers, but not *P. aeruginosa*). It may be useful in patients with risks for these pathogens, particularly in elderly patients who are admitted from nursing homes and patients who have recently received antibiotic therapy. Clinical experience with ertapenem is limited, however. Doxycycline can be used as an alternative to a macrolide, based on minimal-to-moderate experience for treatment of *Legionella* infections [62].

Monotherapy with azithromycin can be considered in selected patients who have nonsevere disease (may be admitted for reasons other than CAP) and do not have risks for DRSP or gram-negative pathogens. Data from two randomized, double-blind studies of adults hospitalized for CAP have demonstrated that parenteral azithromycin monotherapy was as effective as intravenous cefuroxime therapy with or without intravenous erythromycin (the azalide monotherapy regimen had greater tolerability) [63,64]. Feldman et al [65] reviewed the records of patients with CAP who were admitted to a Veterans Affairs facility between December 1997 and July 2001 and compared the outcomes of patients who received azithromycin monotherapy with the outcomes of patients who received ATS-recommended antibiotics or non–ATS-recommended antibiotics. Outcomes included time
to stability, length of stay (LOS), and mortality and were adjusted for severity of illness (mean PSI score: 89.2 for azithromycin group versus 95.0 for the ATS groups; \( P = 0.07 \)) and processes of care. Patients requiring ICU management were excluded. Mortality and re-admission rates were similar among the groups, but mean LOS was shorter in the azithromycin group. None of the 10 patients with erythromycin-resistant \( S \) pneumoniae infections died or was transferred to the ICU, including the six patients who received azithromycin. In a retrospective analysis of the impact of initial antibiotic choice on 30-day mortality rates in patients admitted to the hospital for CAP, Brown et al [66] observed that patients who received monotherapy with macrolides had the lowest mortality rate, but were the least ill. Such patients were younger and were more likely to be in low-risk groups.

Although most admitted patients initially are treated with an intravenous regimen, many patients, particularly those without risk factors for severe pneumonia, can receive oral therapy, especially with highly bioavailable agents such as the quinolones. When an intravenous \( \beta \)-lactam is combined with coverage for atypical pathogens, the addition of a macrolide, doxycycline, or ketolide can be achieved with oral therapy in carefully selected patients without severe pneumonia risk factors.

**Patients in the intensive care unit**

ICU patients are likely to be very ill and have risk factors for more resistant pathogens. In a review of nine studies that included 890 patients with CAP who were admitted to the ICU, the most common pathogens (in order of frequency) were \( S \) pneumoniae, Legionella spp, \( H \) influenza, Enterobacteriaceae, \( S \) aureus, and \( Pseudomonas \) spp. For patients without risks for Pseudomonas infection, coverage for \( S \) pneumoniae and Legionella species should be ensured [13]. The combination of a potent antipneumococcal \( \beta \)-lactam and an advanced macrolide or a respiratory fluoroquinolone should provide an effective spectrum for such patients. The role of monotherapy with a respiratory fluoroquinolone is not yet established for severe CAP, and if the patient has pneumococcal meningitis, the efficacy of quinolone monotherapy is uncertain. If risk factors for Pseudomonas infection are present (or if other infection sites coexist in which Pseudomonas spp or more resistant pathogens are considerations), therapy should include agents that are effective against pneumococcus, Pseudomonas spp, and Legionella spp. Piperacillin–tazobactam, imipenem, meropenem, and ceftapime are the preferred \( \beta \)-lactams when there is concern for unusual pathogens, such as \( P \) aeruginosa or other gram-negative bacteria.

**Switch from intravenous to oral therapy**

Once the patient has a good clinical response to initial therapy, other coexisting medical problems are stabilized, and the patient can eat and drink
again, consideration should be given to switching from intravenous to oral antibiotic therapy. Ramirez et al [67] defined a set of criteria for an early switch from intravenous to oral therapy that included improved cough and dyspnea, fever less than 37.8°C for at least 8 hours, normalized white blood cell count, oral intake, and adequate intestinal function. These criteria are discussed further by Ramirez in another article in this issue.

Alternative or additional antimicrobial therapy of pathogens based on epidemiologic considerations

For several patients, clinicians should be aware of other potential pathogens that are separate from or in addition to the most common organisms for which the empiric therapies in Box 2 are directed. Among these pathogens are respiratory viruses.

Although no prospective, controlled studies of antiviral treatment of viral pneumonias have been reported in adults, antiviral therapy is warranted for influenza, varicella, herpesvirus, and other viruses in selected circumstances (Table 4). In ambulatory adults with influenza, early treatment with inhaled zanamivir or oral oseltamivir seems to reduce the likelihood of lower respiratory tract complications [68–70]. The use of influenza antiviral medications seems to reduce the likelihood of respiratory tract complications as reflected by reduced rates of antibacterial agent use in ambulatory patients with influenza. In one retrospective study of hospitalized adults with influenza, a minority of whom had radiographically documented pneumonia, no obvious benefit of amantadine treatment was found [71]; however, because such patients often have recoverable virus after hospitalization (median duration, 4 days), antiviral treatment seems reasonable. Because of its broad influenza spectrum, low risk for resistance emergence, and lack of bronchospasm risk, oseltamivir is an appropriate treatment choice in hospitalized patients.

Antimicrobial therapies for infection with other pathogens that are associated with epidemiologic conditions are listed in Table 4. Clinicians should consider the importance of the epidemiologic association when choosing these agents and consider the need to provide effective therapy for the core group of pathogens (eg, S pneumoniae and atypical pathogens).

Pathogen-directed therapy

Once the cause of the infection has been identified through reliable microbiologic methods, most experts recommend that antimicrobial therapy be directed to that pathogen and not to the possibility of atypical pathogen co-infection; however, some authorities question this approach in light of recent data [72–74].

Treatment options may be simplified if the etiologic agent is established or strongly suspected (see Table 2). Diagnostic procedures that provide
identification of a specific cause within 24 to 72 hours still can be useful for
guiding continued therapy. If an appropriate culture reveals the isolation of
penicillin-susceptible *S pneumoniae*, therapy can be specified by selecting
a narrow-spectrum agent, such as penicillin or amoxicillin. It is hoped that
this approach reduces the selective pressure for resistance. This information
is often available for consideration if the patient is switched from parenteral
to oral therapy and may be used to direct specific antimicrobial choices.

Several studies suggest that dual therapy that includes an empiric
macrolide reduces the mortality rate associated with bacteremic pneumo-
coccal pneumonia. It is uncertain what the impact of these findings is on the
principle of narrowing the regimen to effective monotherapy once the results
of susceptibilities are known [72–74]. The results of these studies have led to
the suggestion that these observations might result from the presence of
unknown coinfection with an atypical pathogen. An alternative explanation
is the immunomodulatory effects of macrolides. These studies have
significant design limitations, as they are not prospective or randomized.
They evaluated the effects of initial empiric therapy before the results of
blood cultures were known and did not examine the effects of pathogen-
specific therapy after the results of blood cultures were available.

The need to provide pathogen-specific therapy for anaerobic pathogens
in patients with suspected aspiration pneumonia is uncertain. Some studies
have shown that in this setting, patients improve without specific therapy
directed at these pathogens [14].

As MRSA becomes more common in CAP, the most effective therapy will
need to be defined. Most CA-MRSA strains reportedly have been associated
with skin infections, but they also have been associated with pneumonia
(primarily in children, although the authors have observed such cases in adults
during the winter of 2003 to 2004). In general, these strains are more
susceptible in vitro to non–β-lactam antimicrobial drugs than are hospital-
acquired strains. They are often susceptible in vitro to trimethoprim/
sulfamethoxazole and to the fluoroquinolones, although pockets of fluo-
roquinolone-resistant strains exist. They are often susceptible to clindamycin,
but the emergence of resistance during therapy has been reported (especially in
erythromycin-resistant strains). There is insufficient data on the use of these
agents to treat adults with CA-MRSA pneumonia. Until such data become
available, the authors recommend vancomycin or linezolid for initial therapy
of such patients.

**Recommendations for duration of therapy**

Most patients with CAP receive treatment for at least 7 to 10 days, but
few well-controlled studies have evaluated the optimal duration of therapy
for these patients, both in and out of the hospital. Duration is difficult to
define in a uniform fashion, because some antibiotics are administered for
a short time, but have a long half-life at respiratory sites of infection
Table 4
Recommended antimicrobial therapy for specific pathogens

| Organism                  | Preferred antimicrobial drugs | Alternative antimicrobial drugs |
|---------------------------|------------------------------|--------------------------------|
| *S. pneumoniae* Penicillin-nonresistant (MIC <2 μg/mL) | Pencillin G, amoxicillin      | Macrolide, telithromycin, cephalosporins (oral cepodoxime, cefprozil, cefturoxime, cefdinir, cefditoren, parenteralcefuroxime, ceftriaxone, cefotaxime), clindamycin, doxycycline, respiratory fluoroquinolone<sup>a</sup> |
| *S. pneumoniae* Penicillin-resistant MIC ≥2 μg/mL | Agents based on susceptibility, including, cefotaxime, ceftriaxone, fluoroquinolone<sup>a</sup>; telithromycin (orally, only for mild infections) | Vancomycin, linezolid (high-dose amoxicillin, 3 g/d, should be effective for strains with penicillin [MIC ≤4 μg/mL]) |
| *H. influenzae* Non–β-lactamase producing: | amoxicillin                   | Fluoroquinolone<sup>a</sup>, doxycycline; azithromycin<sup>b</sup>, clarithromycin<sup>b</sup> |
| *H. influenzae* β-Lactamase producing: | second- or third-generation cephalosporin, amoxicillin/ clavulanate | |
| *M. pneumoniae/C. pneumoniae* | Macrolide, a tetracycline    | Telithromycin, fluoroquinolone<sup>a</sup> |
| *Legionella spp*         | Fluoroquinolone<sup>a</sup>, azithromycin, clarithromycin | Doxycycline |
| *C. psittaci*            | A tetracycline               | Macrolide |
| *C. burnetti*            | A tetracycline               | Macrolide |
| *Francisella tularensis* | Doxycycline, Gentamicin, streptomycin | |
| *Yersinia pestis*        | Streptomycin, gentamicin     | Doxycycline, fluoroquinolone Other fluoroquinolones, doxycycline; penicillin, if susceptible |
| Anthrax (inhalation)     | Ciprofloxacin                | |
| Enterobacteriaceae       | Third-generation cephalosporin, carbapenem (drug of choice if extended spectrum β-lactamase producer) | β-lactam-β-lactamase inhibitor<sup>c</sup>, fluoroquinolone |
| *P. aeruginosa*          | Antipseudomonal β-lactam<sup>d</sup> plus ciprofloxacin or levofloxacin (750 mg daily) or aminoglycoside | Aminoglycoside plus ciprofloxacin or levofloxacin (750 mg daily) |
| *B. pseudomallei*        | Imipenem, ceftazidime        | Fluoroquinolone, TMP/SMX |
| *S. aureus*              | Methicillin-susceptible: antistaphylococcus penicillin<sup>e</sup> | Cefazolin, clindamycin |
Table 4 (continued)

| Organism                                      | Preferred antimicrobial drugs                      | Alternative antimicrobial drugs                  |
|-----------------------------------------------|---------------------------------------------------|-------------------------------------------------|
| Methicillin-resistantf: vancomycin or linezolidβ-Lactam-β-lactamase inhibitor, clindamycin | Methicillin-resistantf: vancomycin or linezolidβ-Lactam-β-lactamase inhibitor, clindamycin | Methicillin-resistantf: vancomycin or linezolidβ-Lactam-β-lactamase inhibitor, clindamycin |
| Anaerobe (aspiration)                         | Methicillin-resistantf: vancomycin or linezolidβ-Lactam-β-lactamase inhibitor, clindamycin | Methicillin-resistantf: vancomycin or linezolidβ-Lactam-β-lactamase inhibitor, clindamycin |
| Influenza                                      | Oseltamivir or zanamivir (influenza A or B); amantadine or rimantadine (influenza A) | Oseltamivir or zanamivir (influenza A or B); amantadine or rimantadine (influenza A) |
| Mycobacterium tuberculosis                    | Isoniazid plus rifampin plus ethambutol plus pyrazinamide | Isoniazid plus rifampin plus ethambutol plus pyrazinamide |
| Coccidioides immitis                           | Uncomplicated infection in normal host: no therapy generally recommended For therapy: itraconazole, fluconazole | Uncomplicated infection in normal host: no therapy generally recommended For therapy: itraconazole, fluconazole |
| Histoplasma                                    | Itraconazole Amphotericin B                        | Itraconazole Amphotericin B                      |

Choices should be modified based on susceptibility, test results, and advice from local specialists. Refer to local references for appropriate doses.

Abbreviations: ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America; TMP/SMX, trimethoprim/sulfamethoxazole.

a Levofloxacin, gatifloxacin, moxifloxacin (not a first-line choice for penicillin-susceptible strains); ciprofloxacin is appropriate for Legionella spp, and most gram-negative bacilli (including H influenza).

b Azithromycin is more active in vitro than clarithromycin for H influenza.

c Ticarcillin/clavulanate; piperacillin/tazobactam for gram-negative bacilli; ampicillin/sulbactam or amoxicillin/clavulanate is appropriate for oral anaerobes.

d Ticarcillin, piperacillin, ceftazidime, cefepime, aztreonam, imipenem, meropenem.

e Nafcillin, oxacillin fluocoxacillin.

f See text regarding community-acquired MRSA.

g Imipenem/cilastatin, meropenem, ertapenem.

(eg, azithromycin). Most patients become clinically stable within 3 to 7 days, so longer durations of therapy are rarely necessary; however, patients with persistent clinical instability are often readmitted to the hospital and may not be candidates for short-term therapy. Short-term therapy may not be optimal for patients with bacteremic S aureus pneumonia because of the risks for associated endocarditis and deep-seated infection; patients with meningitis-complicating pneumonia; patients with P aeruginosa pneumonia, which is often a necrotizing pneumonia; and patients with infection caused by other less common pathogens. In one study, 8-day therapy of nosocomial pneumonia with P aeruginosa led to relapse more commonly than did 15-day therapy [75]. Studies that defined the duration of therapy focused on patients receiving accurate empiric therapy, and no data exist that well define the duration of treatment in patients who initially received an ineffective therapy regimen.
In trials of antibiotic therapy for CAP, azithromycin was used for 7 to 10 days as monotherapy in admitted patients (intravenous azithromycin for the initial 2–3 days of treatment, with the option of changing to oral treatment to complete the course) and for 3 to 5 days as oral therapy in outpatients. Some reports used one-dose therapy for patients with atypical pathogen infection [44,63,64,76]. The ketolide telithromycin has been used for 5 to 7 days to treat outpatients, including some patients with pneumococcal bacteremia or PSI classes of at least III [77]. The antipneumococcal quinolones have been used for 7 to 14 days in inpatients and outpatients, but most patients have a good clinical response within 2 to 3 days. Two studies of quinolones have shown that using quinolone doses that result in high antipneumococcal activity can lead to a rapid clinical response. In one study, more recipients of 750-mg levofloxacin than recipients of 500-mg levofloxacin became afebrile by day 3 (49.1% versus 38.5%; \( P = 0.03 \)). In that study, the 750-mg dose was successful after only 5 days of therapy [78]. In another study, 58.9% of patients receiving 400 mg of moxifloxacin became afebrile by day 2 (this rate was higher than that for the comparator agent in the study), and 50% of these patients were switched to oral therapy by day 3 [79].

Based on the available data, the authors believe that patients with CAP should be treated for a minimum of 5 days, and therapy should not be stopped until patients are afebrile for 48 to 72 hours and have no more than one clinical instability. Longer durations of therapy may be needed if initial therapy was not active against the identified etiologic pathogen, and longer durations of therapy are needed if there is an extrapulmonary infection, such as meningitis or endocarditis. Patients with documented \textit{S} \textit{aureus} bacteremia, \textit{P} \textit{aeruginosa} pneumonia, or infection caused by several other less common pathogens (eg, \textit{Burkholderia pseudomallei}, fungus) may need longer durations of therapy.

References

[1] Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. Medicine 1990;69:307–16.
[2] Farr BM, Kaiswer DL, Harrison BDW, et al. Prediction of microbial etiology at admission to hospital pneumonia from the presenting clinical features. Thorax 1989;44:1031–5.
[3] Marrie TJ, Peeling RW, Fine MJ, et al. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. Am J Med 1996;101:508–15.
[4] Lieberman D, Schlaeffer F, Boldur I, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax 1996;51:179–84.
[5] Tan MJ, Tan JS, File TM Jr. Legionnaire’s disease with bacteremic coinfection. Clin Inf Dis 2002;35:533–9.
[6] File TM Jr, Plouffe JF Jr, Breiman RF, Skelton SK. Clinical characteristics of \textit{Chlamydia pneumoniae} infection as the sole cause of community-acquired pneumonia. Clin Infect Dis 1999;29:426–8.
[7] File TM Jr. Community-acquired pneumonia. Lancet 2003;362:1991–2001.
[8] deRoux A, Marcos MA, Garcia E, Mensa J, et al. Viral community-acquired pneumonia in nonimmunocompromised adults. Chest 2004;125:1343–51.

[9] Arancibia F, Bauer TT, Ewig S, et al. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. Arch Intern Med 2002;162:1849–58.

[10] Gorak EJ, Yamada SM, Brown JD. Community-acquired methicillin-resistant *Staphylococcus aureus* in hospitalized adults and children without known risk factors. Clin Infect Dis 1999;29:801–2.

[11] Dufour P, Gillet Y, Bes M, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton-Valentine leukocidin. Clin Infect Dis 2002;35:819–24.

[12] Mongkolrattanothai K, Boyle S, Kahana MD, Daum RS. Severe *Staphylococcus aureus* infections caused by clonally related community-acquired methicillin-susceptible and methicillin-resistant isolates. Clin Infect Dis 2003;37:1050–8.

[13] Vergis EN, Akbas E, Yu VL. *Legionella* as a cause of severe pneumonia. Semin Respir Crit Care Med 2000;21:295–304.

[14] El-Solh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. Am J Respir Crit Care Med 2003;167:1650–4.

[15] Ruiz M, Ewig S, Torres A, et al. Severe community-acquired pneumonia: risk factors and follow-up epidemiology. Am J Respir Crit Care Med 1999;160:923–9.

[16] Mandell LA. Clinical relevance of antimicrobial resistance. Semin Respir Infect 2001;16:153–4.

[17] Metlay JP. Update on community-acquired pneumonia: impact of antibiotic resistance on clinical outcomes. Curr Opin in Inf Dis 2002;15:163–7.

[18] File TM Jr. Appropriate use of antimicrobials for drug-resistant pneumonia: focus on the significance of β-lactam-resistant *Streptococcus pneumoniae*. Clin Infect Dis 2002;34(Suppl):S17–26.

[19] Yu VL, Chiu CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis 2003;37:230–7.

[20] Musher DM, Dowell ME, Shortridge VD, et al. Emergence of macrolide resistance during treatment of pneumococcal pneumonia. N Engl J Med 2002;346:630–1.

[21] Kelley MA, Weber DJ, Gilligan P, et al. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. Clin Infect Dis 2000;31:1008–11.

[22] Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. Clin Infect Dis 2002;35:556–9.

[23] Davidson R, Cavalcanti R, Brunton JL, et al. Levofloxacin treatment failures of pneumococcal pneumonia in association with resistance. N Engl J Med 2002;346:747–50.

[24] Kays NB, Smith DW. Levofloxacin treatment failure in a patient with fluoroquinolone resistant *Streptococcus pneumoniae*. Pharmacother 2002;22:395–9.

[25] Anderson KB, Tan JS, File TM Jr, et al. Emergence of levofloxacin-resistant pneumococci in immunocompromised adults after therapy for community-acquired pneumonia. Clin Infect Dis 2003;37:376–81.

[26] Campbell GD Jr, Silverman R. Drug-resistant *Streptococcus pneumoniae*. Clin Infect Dis 1998;26:1188–95.

[27] Clavo-Sanchez AJ, Giron-Gonzalez JA, Lopez-Prieto D, et al. Multivariate analysis of risk factors for infection due to penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae*: a multicenter study. Clin Infect Dis 1997;24:1052–9.

[28] Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. JAMA 2001;286:1857–62.

[29] Jo PL, Tse WS, Tsang KW, et al. Risk factors for acquisition of levofloxacin-resistant *Streptococcus pneumoniae*: a case-control study. Clin Infect Dis 2001;32:701–7.
[30] Ruhe JJ, Hasbun R. *Streptococcus pneumoniae* bacteremia: duration of previous antibiotic use and association with penicillin resistance. Clin Infect Dis 2003;36:1132–8.

[31] Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin Infect Dis 2000;31:383–421.

[32] Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance. Arch Intern Med 2000;160:1399–408.

[33] Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2001;163:1730–54.

[34] Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37:1405–33.

[35] British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults. Thorax 2001;56(Suppl 4):iv1–64.

[36] Matsushima T, Kohno S, Saito A, Japanese Respiratory Society community-Acquired Pneumonia Treatment Guideline Creation Committee. Diagnostic and treatment guideline for community-acquired pneumonia. Tokyo: Japanese Respiratory Society; 2000.

[37] Stahl JE, Barza M, DesJardins J, et al. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. Arch Intern Med 1999;159:2576–80.

[38] Gleason PP, Meehan TP, Fine JM, et al. Association between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 1999;159:2562–72.

[39] Dudas V, Hopeff A, Jacobs R, et al. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann Pharmacother 2000;34:446–52.

[40] Houck PM, MacLehose RF, Niederman MS, et al. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. Chest 2001;119:1420–6.

[41] Bochud PY, Moser F, Erard P, et al. Community-acquired pneumonia: a prospective outpatient study. Medicine 2001;80:75–87.

[42] Falguera M, Sacristan O, Nogues A, et al. Non-severe community-acquired pneumonia: correlation between cause and severity or comorbidity. Arch Intern Med 2001;161:1866–87.

[43] McCracken GH Jr. Current status of antibiotic treatment for *Mycoplasma pneumoniae* infections. Ped Infect Dis J 1986;5:167–71.

[44] Rizzato G, Montemurro L, Fraioli P, et al. Efficacy of a three-day course of azithromycin in moderately severe community-acquired pneumonia. Eur Respir J 1995;8:398–402.

[45] Patel T, Desai R, Duff J, et al. Comparison of grepafloxacin (GFX) with clarithromycin (CLA) in the treatment of community-acquired pneumonia (CAP). Presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 28 to October 1, 1997.

[46] Sullivan J, Gezon J, Williams-Hopkins D, et al. A double blind, randomized multicenter study in ambulatory community-acquired pneumonia (CAP) comparing trovafloxacin with clarithromycin. Presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 28 to October 1, 1997.

[47] O'Doherty B, Muller O. Randomized, multicentre study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate community-acquired pneumonia: Azithromycin Study Group. Eur J Clin Microbiol Infect Dis 1998;17:828–33.

[48] Laurent K. Efficacy, safety and tolerability of azithromycin versus roxithromycin in the treatment of acute lower respiratory tract infections. J Antimicrob Chemother 1996;37(Suppl C):115–24.
Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. Infect Med 1999;16:748–63.

Ramirez JA, Nguyen T-H, Tellier G, et al. Treating community-acquired pneumonia vs twice-daily clarithromycin. J Resp Dis 1999;20:S40–8.

Fogarty C, Goldschmidt R, Bush K. Bacteremic pneumonia due to multidrug-resistant pneumococci in 3 patients treated unsuccessfully with azithromycin and successfully with levofloxacin. Clin Infect Dis 2000;31:613–5.

Lautenbach E, Larosa LA, Kasbekar N, et al. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of, and risk factors for, inappropriate use. Arch Intern Med 2003;163:601–5.

Mushe DM, Bartlett JG, Doern GV. A fresh look at the definition of susceptibility of Streptococcus pneumoniae to β-lactam antibiotics. Arch Intern Med 2001;161:2538–44.

File TM Jr. Telithromycin: the first ketolide. Pharmacy and Therapeutics 2002;27:14–23.

Xiong YQ, Le TP. Telithromycin (HMR 3647): the first ketolide antibiotic. Drugs Today (Barc) 2001;37:617–28.

Hagberg L, Torres A, Van Rensburgy DJ, et al. Efficacy and tolerability of telithromycin vs. high-dose amoxicillin in the treatment of community-acquired pneumonia [abstract]. Presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, September 17–20, 2000.

Tellier G, Hassman J, Leroy B, et al. Oral telithromycin (HMR 3647) 800 mg daily is well tolerated and as effective as oral clarithromycin 500 mg twice daily in community-acquired pneumonia in adults [abstract]. Presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, September 17–20, 2000.

Pullman J, Champlin J, Leroy B, Sidarous E. Oral telithromycin (HMR 3647) 800 mg once daily for 7-10 days is well tolerated and as effective as oral trovafloxacin 200 mg once daily for 7-10 days in community-acquired pneumonia [abstract]. Presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, September 17–20, 2000.

Tice A. Community-acquired pneumonia: recent insights into an old disease. Infections in Medicine 2003;20:352–6.

Ortiz-Ruiz G, Caballero-Lopez J, Friedland IR, et al. A study evaluating the efficacy, safety, and tolerability of ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults [abstract]. Clin Infect Dis 2002;34:1076–83.

Vetter N, Cambroner-Hernandez E, Rohlf J, et al. A prospective, randomized, double-blind multicenter comparison of parenteral ertapenem and ceftriaxone for the treatment of hospitalized adults with community-acquired pneumonia. Clin Ther 2002;24:1770–85.

Martinez FJ, Lynch JP, File TM Jr. Doxycycline for treatment of community-acquired pneumonia: reply. Clin Infect Dis 2002;35:632.

Plouffe J, Schwartz DB, Kolokathis A, et al. Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia: the Azithromycin Intravenous Clinical Trials Group. Antimicrob Agents Chemother 2000;44:1796–802.

Vergis EN, Indorf A, File TM Jr, et al. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients. Arch Intern Med 2000;160:1294–300.

Feldman RB, Rhew DC, Wong JY, et al. Azithromycin monotherapy for patients hospitalized with community-acquired pneumonia: a 31/2 year experience from a Veterans Affairs hospital. Arch Intern Med 2003;163:1718–26.

Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest 2003;123:1503–11.

Ramirez JA. Managing antibiotic therapy of community-acquired pneumonia in the hospital setting: focus on switch therapy. Pharmacotherapy 2001;21:79S–82S.
[68] Kaiser L, Keene ON, Hammond JM, et al. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. Arch Intern Med 2000;160:3234–40.

[69] Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA 2000;283:1016–24.

[70] Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. JAMA 1999;282:1240–6.

[71] Kaiser L, Hayden FG. Hospitalizing influenza in adults. Curr Clin Top Infect Dis 1999;19:112–34.

[72] Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978–1997. Am J Med 1999;107:43S–43S.

[73] Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161:1837–42.

[74] Martinez JA, Horcajada JP, Almeda M, et al. Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36:389–95.

[75] Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290:2588–98.

[76] Schonwald S, Barsic BN, Klinar I, et al. Three-day azithromycin compared with ten-day roxithromycin treatment of atypical pneumonia. Scand J Infect Dis 1994;26:706–10.

[77] Tellier G, Isakov T, Petermann W, Patel M, Lavin B. Efficacy and safety of telithromycin (800 mg once daily) for 5 or 7 days vs clarithromycin (500 mg twice daily) for 10 days in the treatment of patients with community-acquired pneumonia [abstract L-373]. Presented at 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy Abstracts, American Society for Microbiology. San Diego, CA, September 27 to 30, 2002.

[78] Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: new treatment paradigm. Clin Infect Dis 2003;37:752–60.

[79] Finch R, Schurmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. Antimicrob Agents Chemother 2002;46:1746–54.