



special reports

Guidelines for Empiric Antimicrobial Prescribing in Community-Acquired Pneumonia*

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Empiric antimicrobial prescribing for community-acquired pneumonia remains a challenge, despite the availability of treatment guidelines. A number of key differences exist between North American and European guidelines, mainly in the outpatient setting. The North American approach is to use initial antimicrobial therapy, which provides coverage for *Streptococcus pneumoniae* plus atypical pathogens. Europeans tend to focus on providing pneumococcal coverage with less emphasis on covering for an atypical pathogen. Ambulatory patients without comorbidity are more likely to receive macrolide therapy in North America, whereas in Europe these patients would probably receive a β -lactam agent. Major issues that are fundamental to this difference include the importance of providing therapy for atypical pathogens and the clinical significance of macrolide-resistant *S pneumoniae*. Prospective data are required to evaluate which of these two approaches offers clinical superiority. (CHEST 2004; 125:1888–1901)

Key words: antibiotic resistance; community-acquired pneumonia; empiric prescribing; management guidelines

Abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; DRSP = drug-resistant *Streptococcus pneumoniae*; IDSA = Infectious Diseases Society of America; MIC = minimal inhibitory concentration; MRSP = macrolide-resistant *Streptococcus pneumoniae*

Despite major advances in antimicrobial therapy, the empiric treatment of adults with community-acquired pneumonia (CAP) remains a considerable challenge.¹ CAP is a common, but serious, respiratory disease, occurring mostly during the winter, and producing significant morbidity and mortality. Not surprisingly, CAP places tremendous pressure on health-care resources. In the United States, the estimated cost of treatment is > \$20 billion (in US dollars) per year, while in the United Kingdom this annual cost has been calculated to be > £400 million.² In Spain, the cost of hospitalizations alone due to CAP was estimated as \$137 million (in US dollars) per annum in 2001.³

A limited range of key pathogens cause the majority of CAP cases, with *Streptococcus pneumoniae* being the most common.^{4,5} Other etiologic agents include (but are not limited to) *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneu-*

moniae, *Chlamydia pneumoniae*, *Legionella* spp, *Chlamydia psittaci*, *Coxiella burnetii*, enteric Gram-negative bacteria, anaerobes (aspiration pneumonia), and respiratory viruses. For the purposes of this

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review, the atypical pathogens are considered to be *M pneumoniae*, *C pneumoniae*, and *Legionella* spp. Some patients with CAP may have a mixed infection involving both “typical” and “atypical” pathogens or even a viral organism (eg, influenza virus),⁶ although the incidence of such coinfection is not well-known. The incidence/prevalence of atypical pathogens in patients with CAP is not clear, with varying reports on their incidence, probably due to difficulties in the reliable detection of these organisms.⁷

Ideally, a rapid, single test would identify the causative pathogen, allowing the patient to receive pathogen-directed antimicrobial therapy. However,

even when extensive diagnostic testing is used, the causative pathogen cannot be identified in up to 50% of cases.⁶ These methodological limitations mean that clinicians must rely heavily on empiric antibiotic therapy.⁶ The empiric approach to treatment is based on an assessment that one of the key pathogens is likely to be responsible for disease in a particular patient. This is not an easy assessment to make, being dependent on many different variables, including the age of patient, disease severity at presentation, comorbidities (including immune status), site of care (*ie*, inpatient or outpatient), geographic location, travel history, local susceptibility patterns, and the existence of local epidemic modifying factors for drug-resistant *S pneumoniae* (DRSP), or unusual pathogens (Table 1).⁶ Because the condition of a patient with CAP, even in its

mildest form at presentation, has the potential to deteriorate within hours, the prompt initiation of appropriate antibiotic therapy is crucial for a favorable outcome.⁸

Over the last decade or so, professional organizations and societies from many countries have developed guidelines for the empiric treatment of adults with CAP, with the objective of producing a helpful prescribing tool. Although some studies^{9–11} indicate that following guidelines improves patient outcome or reduces the costs associated with CAP, this may not be the case for all patient groups.¹¹ The best of these guidelines are evidence-based, with recommendations made only after extensive review and grading of studies in the literature, and supported by expert opinion. Although, at first glance, guidelines from different countries share common themes, there is considerable variation in the way in which they have been developed. For example, the choice of patient classification schemes, whether or not nursing home residents or immunocompromised patients are included, and specific drug recommendations vary, clearly reflecting local issues.

The primary focus of this article is to compare the specific choices for initial empiric antibiotic treatment in North America and Europe, with the objective of identifying and discussing any major differences. The information used to support the comparisons was obtained from a review of pertinent articles on CAP and a review of consensus statements of guidelines for the management of CAP in adults.^{1,6,12–16} A preference was given for published articles that were evidenced-based, were extensively reviewed with a grading of studies in the literature, and were supported by expert opinion.

NORTH AMERICAN AND EUROPEAN GUIDELINES: A COMPARISON

The key guidelines that have been used in this comparison are summarized in Table 2 and comprise the most recent statements from the American Thoracic Society (ATS),⁶ the Infectious Diseases Society of America (IDSA),¹ the Canadian Infectious Diseases Society/Canadian Thoracic Society,¹² the British Thoracic Society,¹³ the German Respiratory Association/Paul Ehrlich Society for Chemotherapy,¹⁴ the Spanish Respiratory Society/Spanish Society of Chemotherapy,¹⁵ and the French Society of Infectious Diseases.¹⁶ A set of European Respiratory Society guidelines for lower respiratory tract disease also has been published¹⁷ but is not included here. The European Respiratory Society guidelines are not evidence-based, and no distinction is made between acute exacerbations of chronic bronchitis and CAP for outpatient antibiotic treatment.

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Table 1—Empiric Therapy of CAP*

Society/Guideline Type	Outpatient Treatment†	Hospital Treatment‡
North American guidelines		
ATS/evidence-based	No cardiopulmonary disease. No modifying factors: macrolide (eg, azithromycin, clarithromycin) or doxycycline Cardiopulmonary disease ± modifying factors: β-lactam (eg, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate) + (macrolide or doxycycline) or antipneumococcal fluoroquinolone	No cardiopulmonary disease, no modifying factors: azithromycin (IV) or doxycycline + β-lactam or antipneumococcal fluoroquinolone With cardiopulmonary disease ± modifying factors: β-lactam (eg, cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin, IV) + (macrolide or doxycycline, IV or oral) or antipneumococcal fluoroquinolone (IV)
IDSA/evidence-based	Macrolide, doxycycline, or antipneumococcal fluoroquinolone (alternative: β-lactam (eg, amoxicillin/clavulanate, cefuroxime), but these agents not active against atypical pathogens) For older patients with comorbidities, the fluoroquinolone may be a preferred choice	Extended-spectrum cephalosporin + macrolide or β-lactam/β-lactamase inhibitor + macrolide or fluoroquinolone
Canadian Infectious Diseases Society/ Canadian Thoracic Society/evidence-based	Without modifying factors: macrolide or doxycycline With modifying factors and COPD (no recent antibiotics or oral steroids): macrolide (eg, azithromycin or clarithromycin). Recent antibiotics or oral steroids, <i>H influenzae</i> or Gram-negative pathogen suspected: respiratory fluoroquinolone or β-lactam (eg, amoxicillin/clavulanate or second generation cephalosporin) – macrolide cephalosporin + macrolide Suspected macroaspiration pneumonia (anaerobes): β-lactam (eg, amoxicillin/clavulanate) ± macrolide or respiratory fluoroquinolone + (clindamycin or metronidazole) Nursing home resident with suspected <i>S pneumoniae</i> , enteric Gram-negative or <i>H influenzae</i> : respiratory fluoroquinolone or β-lactam (eg, amoxicillin/clavulanate or second-generation cephalosporin) + macrolide	Nursing home resident or suspected <i>S pneumoniae</i> , <i>Legionella pneumophila</i> , or <i>C pneumoniae</i> : respiratory fluoroquinolone or β-lactam (eg, cephalosporin) + macrolide
European guidelines		
British Thoracic Society/ evidence-based	Nonsevere disease: β-lactam (eg, amoxicillin) or macrolide (for patients with β-lactam intolerance)	Nonsevere disease with nonclinical factors for admission: β-lactam (amoxicillin) or macrolide Nonsevere disease: β-lactam (amoxicillin, oral, or ampicillin or benzylpenicillin, IV) + macrolide (oral or IV) or antipneumococcal fluoroquinolone (levofloxacin, oral or IV)
Spanish Respiratory Society/Spanish Society of Chemotherapy/Questionably evidence-based	Mild disease, typical clinical presentation: β-lactam (high-dose amoxicillin) or new-generation fluoroquinolone or macrolide (controlled prescribing due to resistance) Mild disease, atypical clinical presentation: macrolide or new-generation fluoroquinolone	β-lactam (eg, amoxicillin/clavulanate, ceftriaxone, cefotaxime, IV) ± (macrolide or quinolone [eg, ciprofloxacin, oral or IV]) or new-generation quinolone (oral or IV)
French Society of Infectious Diseases/Questionably evidence-based	Ambulatory with mild disease, no comorbidity: β-lactam (eg, high-dose amoxicillin) or antipneumococcal fluoroquinolone (in patients with β-lactam intolerance). For patients < 40 yr old with an atypical clinical picture: macrolide Ambulatory patients with comorbidity, not immediately at risk: <i>Well-defined CAP</i> : high-dose β-lactam (eg, amoxicillin/clavulanate or ceftriaxone, IV) <i>Suspected atypical pathogens</i> : high-dose β-lactam/β-lactamase inhibitor + macrolide or β-lactam (eg, amoxicillin) + ofloxacin or β-lactam (eg, ceftriaxone, IV/IM) + macrolide or new fluoroquinolone <i>Suspected aspiration pneumonia</i> : high-dose β-lactam/β-lactamase inhibitor (IV) or β-lactam (eg, ceftriaxone, IV/IM) + metronidazole (IV)	<i>Well-defined CAP</i> : high-dose β-lactam (amoxicillin/clavulanate or ceftriaxone, IV) <i>Suspected atypical pathogens</i> : high-dose β-lactam/β-lactamase inhibitor + macrolide or β-lactam (eg, amoxicillin) + ofloxacin or β-lactam (eg, ceftriaxone, IV/IM) + macrolide or new fluoroquinolone <i>Suspected aspiration pneumonia</i> : high-dose β-lactam/β-lactamase inhibitor (IV) or β-lactam (eg, ceftriaxone, IV/IM) + metronidazole (IV)
German Respiratory Association/Paul Ehrlich Society for Chemotherapy/ Questionably evidence-based	Younger patients (< 65 yr) without comorbidity: β-lactams (eg, aminopenicillins/β-lactamase inhibitors, cephalosporins), macrolides, antipneumococcal fluoroquinolones (eg, levofloxacin); doxycycline only in special cases Elderly patients and/or patients with comorbidity: β-lactams (eg, aminopenicillins/β-lactamase inhibitors, cephalosporins [eg, cefuroxime, cefotaxime]) or antipneumococcal fluoroquinolone (levofloxacin)	Severe pneumonia in elderly patients with comorbidity: β-lactams (eg, acylaminopenicillins/β-lactamase inhibitors, cephalosporins [eg, cefotaxime, ceftriaxone]) + (macrolide or antipneumococcal fluoroquinolones [eg, levofloxacin]) or β-lactam (carbapenem) + macrolide or fluoroquinolone (eg, ciprofloxacin) + clindamycin

*Key North American and European guidelines.^{1,6,12–16}

†All drugs given orally, unless otherwise indicated.

‡Treatment given on medical ward.

Table 2—Incidences of *M pneumoniae*, *C pneumoniae*, and *Legionella spp* in Hospitalized CAP Patients Around the World*

Pathogen	United Kingdom (n = 1,137)†	Rest of Europe (n = 6,026)‡	Australia and New Zealand (n = 453)§	North America (n = 1,306)
<i>M pneumoniae</i>	10.8 (9–12.6)	6.0 (5.4–6.6)	14.6 (11.3–17.8)	4.1 (3.1–5.3)
<i>C pneumoniae</i>	13.1 (9.1–17.2)	6.3 (5.5–7.3)	3.1 (1.4–6.1)	5.9 (4.3–7.8)
<i>Legionella spp</i>	3.6 (2.6–4.9)	5.1 (4.6–5.7)	7.5 (5.3–10.3)	4.8 (3.7–6.0)

*Values given as mean % (95% confidence intervals). Table adapted with permission from British Thoracic Society.¹³

†Five studies.

‡Twenty-three studies.

§Three studies.

||Four studies.

Across guidelines, recommendations for empiric therapy are based on the pathogens most likely to occur in a given patient group. However, the criteria used for patient stratification in the various guidelines vary. Obviously, specific treatment choices also take into account the cost, side effects, and availability of the various antimicrobial agents. For all of the guidelines, the decision to hospitalize a patient is a priority assessment based on many variables and guided by prognostic scoring systems as well as psychosocial factors. The IDSA guidelines¹ place slightly more emphasis on establishing the etiologic cause of disease (through routine blood cultures, and sputum Gram staining and culture) and the use of pathogen-directed therapy, at least, for all hospitalized patients. The ATS guidelines⁶ and Canadian guidelines¹² are the most definite in associating each patient group with the most likely set of pathogens. Although guidelines generally have moved away from the syndromic approach to treatment (*ie*, prescribing according to typical or atypical clinical presentation), elements of this approach remain in the Spanish guidelines¹⁵ and French guidelines.¹⁶ In North America, the specificity of the syndromic approach has been questioned.¹⁸

The key differences between North American and European guidelines lie in the outpatient setting. A general impression from the North American guidelines is that, from the outset, physicians are looking for broad antimicrobial coverage, and all patients are treated routinely not only for the possible presence of pneumococcal infection but also for the possibility of infection with an atypical pathogen. Thus, for outpatients without comorbidities or risk factors for DRSP, a macrolide agent (or doxycycline as an alternative for patients who are intolerant to macrolide agents) is considered appropriate for first-line therapy. Newer agents (*eg*, azithromycin and clarithromycin) are popular because of better absorption, convenient dosing schedules, and fewer adverse effects compared with older agents (*eg*, erythromycin).¹⁹ The rationale is that these are likely to be

effective against the majority of cases caused by *S pneumoniae* (including most with *mef*-type resistance) as well as the atypical pathogens commonly associated with outpatient CAP (*M pneumoniae* and *C pneumoniae*). By contrast, in the European guidelines, the primary focus of empiric therapy is *S pneumoniae* with less emphasis on the empiric treatment of atypical organisms. Thus, the principal agents recommended are β -lactams, including penicillins. The rationale is that these agents are effective against *S pneumoniae* and, when given in appropriate doses based on pharmacokinetic/pharmacodynamic, remain effective for most strains with reduced penicillin susceptibility. Since most of the macrolide resistance in Europe is *erm*-mediated, which is associated with high-level resistance, the macrolides are not regarded as optimal first-line empiric agents to treat this pathogen if the presence of *S pneumoniae* is considered likely. The syndromic approach used in France and Spain for mild disease defines a group of outpatients with an atypical clinical picture, and macrolide therapy is recommended for these patients.

In North America, outpatients with comorbidities and/or risk factors for DRSP may be prescribed a combination of a β -lactam agent (effective against strains of *S pneumoniae* with higher minimal inhibitory concentrations [MICs]) and a macrolide agent (for coverage of the atypical pathogens), or one of the new fluoroquinolone agents (sometimes referred to as *antipneumococcal fluoroquinolones* or *respiratory fluoroquinolones*). These respiratory fluoroquinolones have a spectrum of activity that includes atypical pathogens as well as macrolide-resistant and penicillin-resistant *S pneumoniae*. In Europe, the recommendations for these patients are less clear-cut (due to differences in patient stratification criteria), although many of them will continue to receive a β -lactam agent (maybe at high dose) as well as, possibly, a macrolide agent (if an atypical pathogen is suspected). The use of fluoroquinolones is fairly restricted in Europe, and these agents are not com-

only used in the outpatient setting. In fact, they are not recommended by the British Thoracic Society¹³ for outpatients at all. With the exception of Germany,¹⁴ doxycycline is not recommended in the European guidelines that were reviewed. In Germany, this agent is recommended only in the case of macrolide intolerance in the treatment of atypical CAP.

For patients requiring hospital admission to a medical ward, North American and European guideline recommendations begin to converge, and it is recommended that most patients in this setting initially receive IV therapy. The view here is that these patients require broader coverage, and that recommended agents must cover both *S pneumoniae* (including consideration for DRSP) and Legionella spp (as well as more unusual pathogens). In North America, the first-line recommendation for these patients is a β -lactam-macrolide combination or one of the new fluoroquinolone agents. In Europe, a high-dose β -lactam-macrolide combination is the widely recommended first-line treatment. New fluoroquinolone agents are beginning to be recommended more frequently throughout Europe in the hospital setting. It has been recommended that all patients admitted to the ICU receive IV therapy. North American guidelines stratify patients into their perceived risk for *Pseudomonas aeruginosa* infection. It is commonly recommended that patients not suspected of having *P aeruginosa* should receive a β -lactam agent (eg, cefotaxime or ceftriaxone) plus a macrolide agent (eg, azithromycin), or a respiratory fluoroquinolone agent (ATS⁶ and Canada¹²). The IDSA¹ recommends the administration of an extended-spectrum β -lactam agent (eg, ampicillin/sulbactam, piperacillin/tazobactam, or cefotaxime/ceftriaxone) plus either a macrolide or a fluoroquinolone agent. For patients in whom *P aeruginosa* is suspected, the first-line recommendations are for a combination of an antipseudomonal fluoroquinolone (eg, ciprofloxacin) plus an antipseudomonal β -lactam, or a triple-therapy combination of an antipseudomonal β -lactam plus an aminoglycoside plus a macrolide. In Europe, ICU patients are treated as a single group, with the most common regimen recommended being a β -lactam plus a macrolide, or a β -lactam plus a new fluoroquinolone with rifampicin added if a Legionella sp is suspected.

DIFFERENCES IN FIRST-LINE RECOMMENDATIONS: POSSIBLE EXPLANATIONS

As highlighted in the previous section, recommendations for empiric therapy in North America and Europe have several key differences, mainly in the

outpatient setting. It is not immediately apparent, however, why this should be the case. In order to shed some light on the differences, the following topics will be discussed below: the clinical impact of pneumococcal CAP and the prevalence of drug-resistant strains; whether North American confidence in monotherapy with macrolides for outpatients is justified; whether European confidence in monotherapy with β -lactams is justified; the clinical importance of atypical pathogens in CAP (ie, prevalence rates and relevance); the consequences of not including coverage for an atypical pathogen; and why the respiratory fluoroquinolones have made such an impact on empiric therapy of CAP in North America.

Clinical Impact of Pneumococcal CAP and the Prevalence of Drug-Resistant Strains

S pneumoniae is the most common causative pathogen of CAP and tends to be associated with more severe disease than that caused by other pathogens.^{20,21} Surveillance studies indicate that the prevalence of DRSP continues to increase worldwide. Many *S pneumoniae* isolates with penicillin resistance exhibit coresistance to macrolides, but macrolide-resistant/penicillin-susceptible strains are also prevalent in some countries (eg, Italy).²² An analysis²³ of European resistance and prescribing data showed a correlation between the greater consumption of newer, long-acting macrolides and increased pneumococcal resistance. Resistance to fluoroquinolones remains low but appears to be slowly rising (ofloxacin, MIC ≥ 8 $\mu\text{g/mL}$).^{24,25}

Is North American Confidence in Macrolides Justified?

Faced with a patient in whom CAP has been diagnosed, all physicians need to consider the possibility of pneumococcal infection. In North America, by recommending a macrolide agent, the conviction is that the agent will work against a possible pneumococcal infection and that macrolide-resistant *S pneumoniae* (MRSP) is not a significant clinical threat in patients with no risk factors or important comorbidities. In addition, this also presumes that there is a need to include coverage for atypical pathogens (discussion follows). In Europe, however, within areas where macrolide resistance in *S pneumoniae* strains has reached a high prevalence (ie, in southern Europe) and is associated with higher MICs, the perception among clinicians is that macrolide agent cannot be used as they are likely to result in therapeutic failure.

Mechanisms of Pneumococcal Macrolide Resistance: Macrolide resistance in *S pneumoniae* is

usually expressed as one of two phenotypes. The first, known as the M phenotype, is due to an efflux pump associated with the *mef(A)* gene. This results in the efflux of macrolides from the cell. M-phenotype isolates typically have low levels of macrolide resistance (erythromycin MIC range, 1 to 32 µg/mL), and are susceptible to lincosamide and clindamycin. The second phenotype, MLSB, results from a ribosomal methylation encoded by the *erm(B)* gene, which blocks the binding of macrolides, lincosamides (eg, clindamycin), and streptogramin B antimicrobial agent. This phenotype is associated with very high-level macrolide resistance (ie, MIC, > 64 µg/mL) and clindamycin cross-resistance.¹⁹ Thus, cross-resistance between clindamycin (MIC, > 0.5 µg/mL) and erythromycin can be used as an approximation of the prevalence of *erm* vs *mef* mechanisms of MRSP.

The rationale to position the macrolides as prominent first-line agents in the North American guidelines is partly based on the perception that the newer macrolide agents (ie, azithromycin or clarithromycin) can be effective against MRSP strains in which lower level resistance results from increased drug efflux with resulting MICs of 1 to 8 µg/mL. In a study reported by Vergis et al,²⁶ a patient with *S pneumoniae* with an azithromycin MIC of 8.0 µg/mL responded to azithromycin monotherapy. This partly explains the difference in the North American and European positioning of macrolides, as the majority of resistance in North America is efflux-mediated (often with MICs of < 16 µg/mL), whereas it is ribosomal (with MICs of > 32 µg/mL) in most locations within Europe. In addition, at the time of the development of the North American guidelines, cases of macrolide failure for outpatients, especially for cases not associated with risks for DRSP, had been infrequent. However, the trend in increasing MICs of the efflux-associated resistant strains in the United States is of significant concern. If these strains with reduced susceptibility become more prevalent in the community and are increasingly associated with clinical failure, reconsideration of the North American recommendations may be required.²⁷

Prevalence of Macrolide Resistance in North America and Europe: The latest report from the Active Bacterial Core Surveillance/Emerging Infections Program Network²² reported that the prevalence of *S pneumoniae* isolates with macrolide resistance (erythromycin, MIC ≥ 1 µg/mL) in the United States had doubled between 1995 and 1999, from 10.6 to 20.4%. The proportion of isolates with the *mef* mechanism was 7.4% in 1995 and 16.5% in 1999, and accounted for the overall increase in macrolide resistance. The erythromycin median MIC increased in isolates using the *mef* mechanism from 4 µg/mL in

1995 to 8 µg/mL in 1999. The proportion of isolates using the *erm* mechanism remained stable at about 3.5%. Data from the SENTRY Antimicrobial Surveillance Program (North America) supported these figures and indicated that, in 1999, macrolide resistance was about 16% in the United States and 9% in Canada.²⁸

The latest update (2001) of the Alexander Project,²⁹ involving 2,483 *S pneumoniae* isolates from the United States, indicated that the prevalence of macrolide resistance among these isolates was 28.3% in 2001. These high prevalence rates were comparable to those found in Spain (26.4%) and Italy (35.9%), although they were not as high as that in France (56.4%). Although prevalence rates in the United Kingdom and Germany remain relatively low (11.5% and 7.5%, respectively), they are continuing to increase. Cross-resistance between clindamycin and erythromycin showed that macrolide resistance in Europe was predominantly due to isolates with the *erm* mechanism, which confers high-level resistance.

Does In Vitro Resistance to Macrolides Lead to Treatment Failure?[?]

The issue of whether *in vitro* macrolide resistance translates into clinical failure remains controversial. While the results of clinical trials suggest that resistance has not compromised clinical efficacy, such trials routinely exclude patients with resistant strains. Furthermore, clinical response alone cannot be used as a measure of antibiotic efficacy. Many patients with mild forms of CAP recover spontaneously, masking any differences between agents.²⁷ Conversely, a significant number of patients die due to the severity of their disease or comorbidities, and not because of the failure of the antimicrobial agent.

Despite the reported increase in clinical failures *in vitro*, the number is relatively low given the extensive use of the macrolide agents. However, the reporting of treatment failure in patients with pneumococcal pneumonia as a result of macrolide use in the outpatient setting appears to be increasing. Three published studies from 2000 and one abstract from 2001 described macrolide treatment failure in 10 patients infected with macrolide-resistant pneumococci. The report from Canada³⁰ described two patients who were hospitalized with pneumococcal bacteremia after receiving routine outpatient clarithromycin treatment. In both cases, the strains of *S pneumoniae* identified had high-level macrolide resistance (erythromycin MICs, 32 and > 256 µg/mL). However, lower level macrolide resistance (ie, through the *mef* mechanism) also has been associated with treatment failure. An article by Kelley et al³¹ in 2000 described the development of

pneumococcal bacteremia in three patients who had been receiving outpatient macrolide therapy (with azithromycin or clarithromycin) and in one patient who had completed azithromycin therapy 3 days prior to the onset of bacteremia. All four of these patients experiencing clinical failure had strains of *S pneumoniae* with low-level resistance (erythromycin MIC range, 8 to 16 $\mu\text{g}/\text{mL}$). Fogarty et al³² reported azithromycin treatment failure in three patients with pneumococcal bacteremia. Two isolates had an MIC of azithromycin of 8 $\mu\text{g}/\text{mL}$, and one was shown to have the *mef* gene. All of these patients had received an oral macrolide agent. Waterer et al³³ reported the failure of IV macrolide therapy that resulted in death. A 49-year-old woman clinically worsened and had bacteremia with a macrolide-resistant pneumococcus while receiving IV azithromycin. Further support for the clinical significance of macrolide resistance was provided by Lonks et al³⁴ in a case-control study that included 86 patients in whom pneumococcal bacteremia was due to an erythromycin–non-susceptible isolate. The control subjects were patients with an erythromycin-susceptible pneumococcal bacteremia matched for age, sex, location, and year of bacteremia. A total of 19 patients with bacteremia caused by an erythromycin-resistant isolate were receiving a macrolide agent compared with none of the matched control subjects ($p < 0.0001$). Of the 19 *S pneumoniae* isolates from the patients with breakthrough bacteremia, 13 had the MLSB phenotype (Spain, 11 patients; United States, 2 patients), and 6 had the M phenotype (all from the United States).³⁴ When data including only patients with M phenotype pneumococcal bacteremias were analyzed, 6 of 28 case patients (21%) and none of the 52 matched control subjects were taking a macrolide at the time of onset of bacteremia ($p = 0.00053$).³⁴ Eighteen of the 19 patients were treated successfully with a β -lactam antibiotic, and 1 patient was treated for a β -lactam allergy with vancomycin. Thus, in this study, breakthrough bacteremia occurred with both *mef*-mediated and *erm*-mediated erythromycin–non-susceptible pneumococci. While it is to be expected that macrolide treatment failures would be predicted in cases of infections caused by strains harboring the *erm* gene, it has been postulated that the high intracellular levels achieved by azithromycin and some macrolides are sufficient to offset the macrolide resistance levels determined by the *mef* gene if the MIC of erythromycin is $< 8 \mu\text{g}/\text{mL}$. However, treatment failures with either a macrolide or an azalide agent have now been reported with strains known to contain the *mef* gene or the M phenotype and, by Lonks et al,³⁴ with strains with MICs of erythromycin as low as 4 $\mu\text{g}/\text{mL}$ mediated by the *mef*

gene. In addition, therapy with azithromycin and clarithromycin has failed against *mef(A)* strains in murine models of *S pneumoniae*.^{35,36}

Most recently, the emergence of resistance to macrolide agents during treatment has been reported. A previously healthy 28-year-old man with severe pneumococcal pneumonia was treated with IV azithromycin (macrolide-susceptible). After initial improvement, his condition suddenly deteriorated, and the patient died. Although the pneumococcal isolate was initially fully susceptible to macrolide agents, at the time of relapse the isolate was resistant to azithromycin with a MIC of 4 $\mu\text{g}/\text{mL}$. A mutation in the gene for ribosomal protein L22 was demonstrated.³⁷

Is European Confidence in β -Lactams Justified?

Given the data supporting the clinical relevance of *in vitro* macrolide resistance, it seems reasonable to examine whether *in vitro* resistance to β -lactam agents also may have clinical implications. In Europe, confidence in β -lactam therapy (at least for amoxicillin and certain parenteral cephalosporins, such as ceftriaxone and cefotaxime) remains high, and these agents routinely constitute first-line recommendations for empiric treatment throughout the outpatient and inpatient setting (usually in combination with a macrolide in hospitalized patients). According to the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group, standard-dose β -lactam agents provide an effective option against *S pneumoniae* CAP caused by either penicillin-susceptible isolates (*ie*, MICs $\leq 0.06 \mu\text{g}/\text{mL}$) or penicillin-intermediate isolates (*ie*, MIC range, 0.1 to 1 $\mu\text{g}/\text{mL}$).²⁰ The dilemma about the continued efficacy of β -lactam agents arises only for those isolates with MICs of $\geq 2 \mu\text{g}/\text{mL}$. Fortunately, the prevalence of *S pneumoniae* strains with MICs of $> 2 \mu\text{g}/\text{mL}$ remains uncommon, and penicillin resistance appears to be stabilizing,²⁸ although MICs of $\geq 4 \mu\text{g}/\text{mL}$ are more common in some geographic areas of high penicillin resistance prevalences, such as France, ([MIC $\geq 4 \mu\text{g}/\text{mL}$] 6.7% in 2001), Spain (18.9%), and the United States (8.6%).²⁹

The literature contains conflicting reports about the clinical efficacy of β -lactams in the treatment of CAP caused by resistant *S pneumoniae* isolates. In some cases, this may be due to inconsistencies in classifying isolates as *resistant*. In 1995, Pallarès et al³⁸ showed that the risk of mortality associated with benzylpenicillin or ampicillin treatment of DRSP pneumonia was similar whether or not patients were infected with a resistant isolate. However, many of their resistant isolates had a MIC of $\leq 1 \mu\text{g}/\text{mL}$, a level which would, today, be considered intermedi-

ate. A more recent report³⁹ studied the impact of penicillin resistance in hospitalized patients with pneumococcal pneumonia, determining that 10.5% of strains were resistant to penicillin (MIC > 1 µg/mL) and that 15.3% of strains showed intermediate resistance to cefotaxime (MIC 1 µg/mL). Patients were treated with either amoxicillin with or without clavulanate (3 g/d) or an injectable cephalosporin. No significant difference in global mortality was found between the penicillin-susceptible group and the penicillin–non-susceptible group.

A retrospective study by Turett et al⁴⁰ in 432 patients with pneumococcal bacteremia, indicated that the risk of mortality was increased if patients had DRSP (MIC ≥ 2 µg/mL). However, as half of the patients had a documented HIV infection, these data cannot be assumed to be representative of the general population. Furthermore, the investigators did not adjust for early death (*ie*, within 2 to 4 days of hospitalization), and many of the patients were treated with vancomycin and/or ceftriaxone, and not a penicillin. Outcomes were available for 32 of the 33 patients with penicillin–non-susceptible pneumococci. Only two of these patients were treated with a penicillin. One was a pediatric patient treated with amoxicillin, and the other was an elderly man who received a single dose of ticarcillin/clavulanate and died. Although the work of Feikin et al⁴¹ suggested that, after taking disease severity into account, patients infected with high-level DRSP (*ie*, penicillin MIC ≥ 4 µg/mL or cefotaxime MIC ≥ 2 µg/mL) had poorer clinical outcomes, the study did not contain any information on severity of illness on presentation or consider whether the treatment regimen was appropriate. Pharmacodynamic studies show that, for β-lactam agents, the duration of the dosing interval for which serum levels exceed the MIC is predictive of bacteriologic efficacy. For optimal effect, this should be ≥ 40%.⁴² By achieving drug concentrations of a β-lactam above the MIC of the organism for at least 40% of the dosing interval, high bacteriologic efficacy is predicted.⁴³ A 2001 prospective study⁴⁴ compared therapies using high-dose amoxicillin/clavulanate with that using high-dose ceftriaxone in 378 patients hospitalized with moderate-to-severe CAP, and 116 evaluable patients had a documented pneumococcal infection. The number of penicillin-resistant (*ie*, MIC ≥ 2 µg/mL) isolates were comparable in the two treatment groups, but the investigators found that no differences in outcome were attributable to differences in penicillin susceptibility. Patients in both treatment groups had good clinical outcomes.

To deal with the problem of increasing *S pneumoniae* MICs, the initial data on a new, pharmacokinetically enhanced formulation of amoxicillin/clavulanate

(2000/125 mg), which was designed to maximize the time spent above the minimal inhibitory concentration for at least 50% of the dosing interval to eradicate *S pneumoniae* isolates with amoxicillin MICs of ≤ 4 µg/mL, have shown it to be effective in therapy for respiratory infections (including CAP) due to *S pneumoniae*, with penicillin MICs ≤ 8 µg/mL.⁴⁵

Present data suggest that CAP caused by isolates of *S pneumoniae* that were considered to be intermediately resistant (*ie*, MIC range, 0.1 to 1.0 µg/mL) should respond well to treatment with a β-lactam agent used in appropriate doses. Therapeutic failures are more likely to occur at higher levels of resistance (*ie*, MIC > 2 µg/mL). Thus, in summary, it is clear that β-lactam agents still have an important role to play in the empiric treatment of CAP due to *S pneumoniae*, provided that these are dosed adequately.

Clinical Importance of Atypical Pathogens in CAP

One of the driving factors in the North American guidelines is the perception that the prevalence of atypical pathogens as etiologic agents in CAP is high. Consequently, recommendations for empiric therapy always include an antimicrobial agent regimen that provides atypical coverage. The rationale is that these organisms are becoming more commonly recognized in some studies as an etiology of CAP, and in the observational studies of therapy for patients who require hospitalization,^{6,46–50} antimicrobial regimens that have activity against the atypical pathogens have been associated with better outcomes. Although these findings are not definitive, they support a potentially important role for the atypical pathogens. The prominent role of therapy with macrolide agents in the North American guidelines is based on the relative frequency of atypical pathogens, and on the concept that it is difficult to differentiate the etiology (*ie*, atypical vs *S pneumoniae*) from the clinical and radiographic findings at presentation.

Thus, for both outpatients and inpatients, the option of using a macrolide, either as monotherapy in otherwise healthy individuals or as part of a combination regimen in patients with risk factors for poor outcomes, is one of the recommendations variably included in the North American recommendations.

By contrast, in Europe, empiric therapy for CAP is based on the need to provide pneumococcal coverage, rather than on the coverage of atypical pathogens. There appears to be a perception among European physicians that the consequences of not providing coverage for CAP due to atypical pathogens (excluding *Legionella* spp) is relatively unim-

portant compared with treating a pneumococcal infection with a macrolide in an area where the prevalence of MRSP is high. The British Thoracic Society guidelines do not recommend the use of the term *atypical pneumonia*, however, they do refer to infections caused by *M pneumoniae*, *C pneumoniae*, *C psittaci*, and *C burnetii* as "atypical." Furthermore, they suggest that, as *M pneumoniae* exhibits epidemic periodicity every 4 to 5 years and largely affects younger persons, a policy for initial empiric therapy that aimed always to cover this pathogen was unnecessary.

The prevalence of atypical pathogens (*M pneumoniae*, *C pneumoniae*, and *Legionella* spp) in patients with CAP remains unclear, not least in part because in practice the specific etiology is established in only a minority of cases and because their rate of identification in CAP varies dramatically between studies. The prevalences of atypical pathogens depend on a variety of factors, including the diagnostic tests and serologic criteria used, and the patient population studied, as well as geographic and temporal variations.⁶ Although the frequency of CAP caused by atypical pathogens appears to have increased over the last few years, this may simply be due to more careful and complete diagnostic evaluations.⁵¹ Methodological difficulties continue to complicate the identification of atypical pathogens. Diagnostic testing for these pathogens is not routinely performed, as culturing is difficult, time-consuming, and requires significant expertise. A microbiological diagnosis based on high acute antibody titers is quick but inaccurate, while diagnosis using the paired serology approach is more accurate but requires > 1 week to perform.⁵²

Atypical Etiology: Outpatients: Those studies that have attempted to identify causative pathogens in CAP patients treated in the community indicate that etiology remains unknown in > 50% of cases. While it is theoretically possible that the absence of any detectable etiology may reflect the importance of atypical pathogens in this population, the data suggest that such patients may actually have an infection with *S pneumoniae* or *H influenzae*.^{53,54} Nevertheless, the role played by *M pneumoniae* and *C pneumoniae* in the outpatient setting has been recognized increasingly over the last few years.^{6,53,55-58}

Atypical Etiology: Hospitalized Patients: Similarly to the outpatient population, etiology remains unknown in a high proportion of cases. Also, very few studies have looked specifically at the prevalence rates of atypical pathogens causing CAP in patients admitted to the ICU.⁵¹ On the basis of a review of 15

published studies over three decades from North America, up to 10% of patients, of all ages, requiring hospitalization for CAP were reported to have infections with *Legionella* spp, *M pneumoniae*, or *C pneumoniae*.⁶ Other American studies^{59,60} suggest an incidence as high as 40 to 60% for these atypical pathogens, sometimes as part of a mixed infection, although these findings have not been universally supported. A study⁵⁴ of patients hospitalized for CAP in Spain sought to address the issue of undefined causative agents, which occur in approximately 50% of patients with CAP using conventional diagnostic methods (*ie*, blood and sputum cultures, and serologic studies). The investigators performed microbiological, genetic, and antigen tests for common respiratory pathogens in lung aspirates obtained from 109 patients by transthoracic needle aspiration. The results demonstrate that this procedure increased the known bacterial etiology from 50 to 83% and, specifically, resulted in the following rank order of pathogens: *S pneumoniae* (30%); *M pneumoniae* (22%); and *C pneumoniae* (13%). This suggested that while *S pneumoniae* remains the most common cause of CAP requiring admission to the hospital, both *M pneumoniae* and *C pneumoniae* are also important. Table 2 highlights the incidences of atypical pathogens in hospitalized CAP patients from studies conducted in the United Kingdom, Europe, Australia and New Zealand, and North America.¹³ Incidences of these pathogens will vary based on the age group, geographic location, and whether an epidemic is occurring at the time of evaluation.⁷

Mixed Infections: Multiple pathogens can be isolated from CAP patients, and virtually all combinations have, at some point, been found.⁶¹ Generally, coinfection is thought to be more prevalent in patients in whom one of the pathogens is atypical, although the frequency and precise nature of mixed infections (either concurrent or sequential) involving atypical pathogens in CAP is not entirely clear (again, this probably is related to the presence of variable diagnostic methods). Some studies using serologic evidence report an incidence of up to 48% among hospitalized patients with CAP.⁶⁰ File et al⁶² found that 45% of patients with *C pneumoniae* were coinfecting with other pathogens, with the most common being pneumococcus.

Clinical Impact of CAP Caused by Atypical Pathogens

While it is well-recognized that Legionnaire disease is often associated with high morbidity and mortality, the clinical course of infections due to *M pneumoniae* and *C pneumoniae* is varied.^{62,63} In-

deed, many of these infections are subclinical or self-limited. And when disease occurs, these pathogens are associated with relatively low mortality rates, particularly among young, ambulatory patients without comorbidity. Although the course of *M pneumoniae* or *C pneumoniae* disease is often self-limiting, it has been reported that these pathogens can cause both mild and severe CAP.^{65–67} The importance of therapy for Mycoplasma and Chlamydia infections has been the subject of some conjecture. A common view is that, especially for mild infections, antimicrobial therapy for atypical pathogens has a minimal impact on clinical outcomes, as many infections are self-limiting. Nevertheless, studies from the 1960s indicate that treatment for mild *M pneumoniae* infections reduces the morbidity of pneumonia and shortens the duration of symptoms.⁷ By contrast, Legionella spp are usually associated with severe disease frequently requiring ICU admission.

The consequences of not covering for Legionella spp infection are generally far more serious than for Mycoplasma or Chlamydia infection, and empiric therapy for patients with severe CAP (irrespective of age) always should cover for this pathogen. As North American guidelines recommend coverage of atypical pathogens (in the inpatient or outpatient setting), even patients with mild disease are likely to be treated for Legionella spp. In Europe, empiric coverage of Legionella spp is provided in accordance with patient stratification criteria (*ie*, in patients with an “atypical clinical picture” or in hospitalized patients). The severity of disease is the key factor that dictates the initial empiric therapy in the European setting.

The clinical importance of a mixed infection is unclear. Some investigators claim that it complicates the course of disease, although this view is not supported by all studies.⁶ From the perspective of recommendations for empiric therapy, addressing the question of whether infection with one pathogen simply facilitates the penetration of a second or whether both pathogens cause symptoms remains a concern.⁶² In their initial broad approach to treatment, North American guidelines, by default, address the possibility of a mixed infection. As atypical pathogens are not empirically covered by European clinicians, the possibility of a mixed infection would be unlikely to have an impact on the current prescribing recommendations.

Why Have the Respiratory Fluoroquinolones Made Such an Impact in North America?

The antimicrobial spectrum of activity (*ie*, Gram-positive, Gram-negative, and atypical pathogens) of the newest, respiratory fluoroquinolones (*eg*, levofloxacin, moxifloxacin, and gatifloxacin) is well-suited

to the North American approach of recommending broad initial coverage for *S pneumoniae* and the atypical pathogens in CAP.⁶⁸ Furthermore, these agents have a number of advantageous pharmacokinetic properties, including excellent penetration into the lung and high oral bioavailability.⁶⁸ The possibility of once-daily dosing is an attractive option. As it is possible to achieve comparable serum levels with either oral or IV therapy, certain patients with moderate disease may be managed in the outpatient setting rather than in the hospital.⁶ Additionally, hospitalized patients may be switched more rapidly from IV to oral therapy, allowing them to be discharged from the hospital early.⁶ These possibilities clearly have economic as well as social advantages. For outpatients with comorbidities and/or risk factors for DRSP, and for patients requiring hospitalization, therapy with respiratory fluoroquinolone agents is increasingly replacing that with a β -lactam-macrolide combination in North America. Perhaps their greatest asset of the latter is their potency against the pneumococcus.⁶⁸ The Canadian guidelines¹² note that, at the time the guidelines were being prepared, there were 14 randomized controlled trials in which therapy with a respiratory fluoroquinolone was compared with standard therapy to treat CAP. In 4 of these 14 studies, there was a statistically significant advantage in favor of the respiratory fluoroquinolone.¹² A retrospective study⁴⁹ found that fluoroquinolone monotherapy was associated with increased survival compared with macrolide or β -lactam monotherapy in patients requiring hospitalization. As the numbers of patients involved were small, however, these data need to be interpreted with caution.

European clinicians clearly have a more reserved approach to the use of the respiratory fluoroquinolones. To some extent, this may be because some of the newer agents are not yet available. Europeans also continue to have confidence in appropriately dosed β -lactams for DRSP (*ie*, mainly amoxicillin, cefotaxime, and ceftriaxone) and prefer to combine a β -lactam with a macrolide for patients in whom the presence of a clinically important atypical pathogen (*ie*, Legionella spp) may be a possibility. There is also a widely held view among European infectious disease, respiratory, and microbiology specialists that the routine recommendation of a respiratory fluoroquinolone for the treatment of CAP would lead to the widespread and inappropriate prescribing of these agents, by primary care practitioners, for anyone with a possible lower respiratory tract infection. The predominant view in North America is that it is not the use of respiratory fluoroquinolones for the treatment of true CAP that is driving resistance, but

rather the inappropriate use for “nonspecific viral” respiratory tract infections.

Resistance to Respiratory Fluoroquinolones: A growing concern in North America is the potential for the fluoroquinolones to provoke resistance mechanisms in *S pneumoniae*. Although the worldwide prevalence of resistance to the fluoroquinolones in *S pneumoniae* remains low (1.2% of strains with ofloxacin MICs of $\geq 8 \mu\text{g/mL}$ in 2001),²⁹ in countries where these agents are more widely used (eg, Canada), resistance (defined as ciprofloxacin MICs $\geq 4 \mu\text{g/mL}$) has increased markedly.^{69–71} The overall prevalence of levofloxacin resistance (levofloxacin MIC $> 4 \mu\text{g/mL}$) in Hong Kong in 2000 increased to 13.3%. By using pulse-field gel electrophoresis, the authors showed that this was associated with the pan-regional dissemination of a fluoroquinolone-resistant variant of the globally distributed Spanish 23F-1 clone.⁷⁰ Thus, the high rate of resistance noted in this study is, to a great extent, due to clonal spread by means of person-to-person transmission in hospitals or nursing homes.^{70,71} Increases in respiratory fluoroquinolone resistance are probably related to the increased use of certain nonrespiratory fluoroquinolones (eg, ciprofloxacin) that have only marginal activity against *S pneumoniae*.^{69,72} In a study by Chen et al,⁶⁹ which showed an increase in fluoroquinolone-resistant *S pneumoniae* in association with an increase of fluoroquinolone usage, the predominant fluoroquinolone used in the Canadian health system during the time of the study was ciprofloxacin. Levofloxacin was the first of the respiratory fluoroquinolones to be introduced into the United States in 1997. Although there is no widespread resistance in any major national study with respect to levofloxacin and *S pneumoniae*, anecdotal treatment failures have been reported.^{24,73,74} Respiratory fluoroquinolones that are highly active against pneumococcus appear less likely to select for resistant strains of *S pneumoniae*.²⁴ From a clinical perspective, therefore, the ATS guidelines support the use of the most potent respiratory fluoroquinolones.

CONCLUSIONS

Empiric prescribing for CAP remains a challenge, despite the availability of treatment guidelines. A number of key differences exist between North American and European guidelines, mainly in the outpatient setting. The North American approach is to use broad initial coverage, and all patients are routinely covered for infection by *S pneumoniae* plus an atypical pathogen. Europeans tend to focus on providing pneumococcal coverage with less emphasis

on covering for an atypical pathogen. Ambulatory patients without comorbidities are likely to receive a macrolide in North America. In Europe, these patients will probably receive a β -lactam.

The prevalence of macrolide resistance in patients with *S pneumoniae* infection continues to rise worldwide. In the United States, the prevalence of these strains has doubled since 1995. Reports of treatment failure with macrolides are accumulating, and empiric recommendations for macrolides may have to be reevaluated based on local *S pneumoniae* resistance. Penicillin resistance in *S pneumoniae* does not appear to have an important clinical impact but may be significant if MICs are $\geq 4 \mu\text{g/mL}$.

The major difference in the positioning of the macrolides remains the difference in resistance mechanisms between North America (*mef*) and Europe (*erm*). The trend of increasing macrolide MICs of *S pneumoniae* strains with the *mef* mechanism may require reconsideration of the North American recommendations, especially if clinical failures continue to be observed.

While the role of atypical pathogens in CAP appears to be established among North American investigators, their importance in Europe continues to be debated partly due to diagnostic difficulties. Disease caused by *M pneumoniae* or *C pneumoniae* is thought frequently to be self-limiting, and not all investigators think that coverage against these pathogens is necessary.

The panel of authors concluded from their extensive review that guidelines vary, in part, because the necessary data for decision making is not available. They recommended that a large outpatient study in patients with mild-to-moderate CAP comparing an oral β -lactam agent (European preference) with an oral macrolide (North American preference) should be performed to determine which of the two approaches offers clinical superiority. This should address the issues of covering for atypical pathogens and the clinical relevance of resistance in those patients with a documented pneumococcal infection. Rather than monitoring the response at 14 and 28 days, the study should address how rapidly symptoms resolve. The study should include the daily response to such parameters as duration of cough, fever, and days to return to work, and should include accurate testing for atypical pathogens as well as typical pathogens so as to define the etiology in patients.

New, respiratory, fluoroquinolone agents are widely used in North America, in many places rapidly replacing the β -lactam-macrolide combination. *S pneumoniae* resistance to these fluoroquinolones is currently low in the United States but is rising in countries with increased use of these agents. This may be due to the use of agents with only

marginal activity against the pneumococcus. ATS guidelines suggest that respiratory fluoroquinolones with the greatest potency against *S pneumoniae* should be the agents of choice.

These agents can be considered appropriate choices for empiric therapy for outpatients with risk factors for DRSP. These factors include the following: age (> 65 years); recent hospitalization or antimicrobial use; presence of children within the household who attend daycare centers; and multiple comorbid conditions.⁷⁵ Ongoing surveillance into the prevalence of DRSP and its clinical impact should assist clinicians in tailoring empiric therapy to current patterns of susceptibility.

The appropriate interpretation of clinical trials and published evidence on the relevance of *in vitro* break points with *in vivo* response will dictate future recommendations on macrolides and other classes of antimicrobial agents used for the treatment of CAP.

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REFERENCES

- Bartlett JG, Dowell SF, Mandell LA, et al. Guidelines from the Infectious Diseases Society of America: practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000; 31:347–382
- Brown PD, Lerner SA. Community-acquired pneumonia. *Lancet* 1998; 352:1295–1301
- Monge V, San-Martin VM, Gonzalez A. The burden of community-acquired pneumonia in Spain. *Eur J Public Health* 2001; 11:362–364
- Green DS, San Pedro G. Empiric therapy of community-acquired pneumonia. *Semin Respir Infect* 2000; 15:227–233
- Lange M. Community-acquired pneumonia: an approach to antimicrobial therapy. *Allergy Asthma Proc* 2000; 21:33–38
- American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med* 2001; 163:1730–1754
- File TM, Tan JS, Plouffe JF. The role of atypical pathogens: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* in respiratory infection. *Infect Dis Clin North Am* 1998; 12:569–592
- Chan CKN, Shibl A, Memish Z, et al. Community-acquired pneumonia (CAP): an update. *J Chemother* 2001; 13(suppl): 23–27
- Dean NC, Silver MP, Bateman KA, et al. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. *Am J Med* 2001; 110:451–457
- Niederman MS. Guidelines for the management of community-acquired pneumonia. *Med Clin North Am* 2001; 85: 1493–1501
- Gleason PP, Kapoor WN, Stone RA, et al. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *JAMA* 1997; 278:32–39
- 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
- British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults. *Thorax* 2001; 56(suppl):1–64
- Paul Ehrlich Society for Chemotherapy and the German Respiratory Society. Rational treatment of bacterial respiratory tract infections. *Chemother J* 2000; 9:3–23
- Dorcar J. Guidelines for community-acquired pneumonia in Spain: another perspective. *Clin Pulm Med* 2000; 7:1–8
- French Society of Infectious Diseases (SPILF). What should the initial antibiotherapy for acute community-acquired pneumonia be? How should it be reassessed in case of failure, given the evolution of responsible pathogens and the resistance of pneumococci? Should combined treatment be used? *Med Mal Infect* 2001; 31:357–368
- European Respiratory Society, European Study on Community-Acquired Pneumonia (ESOCAP) Committee. Guidelines for management of adult community-acquired lower respiratory tract infections. *Eur Respir J* 1998; 11:986–999
- Mulazimoglu L, Yu VL. Can Legionnaires' disease be diagnosed by clinical criteria? A critical review. *Chest* 2001; 120:1049–1053
- Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA* 2001; 286:1857–1862
- Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance. *Arch Intern Med* 2000; 160:1399–1408
- Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA* 1996; 275:134–141
- Felmingham D, Gruneberg RN. The Alexander Project 1996–1997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. *J Antimicrob Chemother* 2000; 45:191–203
- Baquero F. Evolving resistance patterns of *Streptococcus pneumoniae*: a link with long-acting macrolide consumption? *J Chemother* 1999; 11:35–43
- Davidson R, Cavalcanti R, Brunton JL, et al. Levofloxacin treatment failures of pneumococcal pneumonia in association with resistance. *N Engl J Med* 2002; 346:747–750
- Ho PL, Yung RWH, Tsang DNC, et al. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a Hong Kong multi-centre study in 2000. *J Antimicrob Chemother* 2001; 48:659–665
- Vergis EN, Indorf A, File TM, et al. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients; a prospective randomized trial. *Arch Intern Med* 2000; 160: 1294–1300
- Garau J. Clinical failures: the tip of the iceberg? *Respir Med* 2001; 95(suppl):S5–S11
- Hoban DJ, Doern GV, Fluit AC, et al. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin Infect Dis* 2001; 32(suppl):S81–S93
- Alexander Project. Available at: www.Alexander-Network.com. Accessed November 2002
- Deligne B, Turgeon PL, Fleury C, et al. Are macrolides still appropriate for empiric therapy of community-acquired pneumococcal pneumonia [abstract]? The 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago IL, September 22–25, 2001; abstract L-1849
- Kelley MA, Weber DJ, Gilligan P, et al. Breakthrough pneumococcal bacteraemia in patients being treated with

- azithromycin and clarithromycin. *Clin Infect Dis* 2000; 31:1008–1011
- 32 Fogarty C, Goldschmidt R, Bush K. Bacteremic pneumonia due to multi-drug resistant pneumococci in 3 patients treated unsuccessfully with azithromycin and successfully with levofloxacin. *Clin Infect Dis* 2000; 31:613–615
 - 33 Waterer GW, Wunderink RG, Jones CB. Fatal pneumococcal pneumonia attributed to macrolide resistance and azithromycin monotherapy. *Chest* 2000; 118:1839–1840
 - 34 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; 35:556–564
 - 35 Mitten MJ, Meulbroek J, Nukkala M, et al. Efficacy of ABT-337 against experimental bacteremia infections. *Antimicrob Agents Chemother* 2001; 45:2585–2593
 - 36 Girard D, Mathieu HW, Finegan SM, et al. *In vivo* antibacterial activity of CP-654, 743, a new C2-fluoroketolide against macrolide-resistant pneumococci and *Haemophilus influenzae* [abstract]. The 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17–20, 2000; abstract 1816
 - 37 Musher DM, Shortridge VD, Jorgensen JH, et al. Emergence of macrolide resistance during treatment of pneumococcal pneumonia. *N Engl J Med* 2002; 346:630–631
 - 38 Pallarès R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med* 1995; 333:474–480
 - 39 Bedos J, Chardon H, Jehl F, et al. Impact of penicillin resistance in community-acquired pneumococcal pneumonia in adult hospitalized patients: findings of a French national prospective survey [abstract]. The 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago IL, September 22–25, 2001; abstract L-851
 - 40 Turett GS, Blum S, Fazal BA, et al. Penicillin resistance and other predictors of mortality in pneumococcal bacteraemia in a population with high human immunodeficiency virus seroprevalence. *Clin Infect Dis* 1998; 29:321–327
 - 41 Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. *Am J Public Health* 2000; 90:223–229
 - 42 Woodnutt G, Berry V. Two pharmacodynamic models for assessing the efficacy of amoxicillin-clavulanate against experimental respiratory tract infections caused by strains of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 1999; 43:29–34
 - 43 Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibiotic dosing in mice and men. *Clin Infect Dis* 1998; 26:1–12
 - 44 Roson B, Carratala J, Tubau F, et al. Usefulness of beta-lactam therapy for community-acquired pneumonia in the era of drug-resistant *Streptococcus pneumoniae*: a randomized study of amoxicillin-clavulanate and ceftriaxone. *Microb Drug Resist* 2001; 7:85–95
 - 45 File TM Jr, Jacobs MR, Michael D, et al. Outcome of treatment of respiratory tract infections due to *Streptococcus pneumoniae*, including drug-resistant strains, with pharmacokinetically enhanced amoxicillin/clavulanate. *Int J Antimicrob Agents* 2002; 20:235–247
 - 46 Stahl JE, Barza M, DesJardin 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; 159:2576–2580
 - 47 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; 159:2562–2572
 - 48 Dudas V, Hopef 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; 34:446–451
 - 49 Houck PM, MacLeHose RF, Niederman MS, et al. Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 western states: 1992, 1995, and 1997. *Chest* 2001; 119:1420–1426
 - 50 Vergis EN, Yu VL. New directions for future studies of community-acquired pneumonia: optimising impact of patient care. *Eur J Clin Microbiol Infect Dis* 1999; 18:847–851
 - 51 File TM Jr, Plouffe JF Jr, Breiman RF, et al. Clinical characteristics of *Chlamydia pneumoniae* infection as the sole cause of community-acquired pneumonia. *Clin Infect Dis* 1999; 29:426–428
 - 52 Honeybourne D. Community-acquired pneumonia in ambulatory patients: relative importance of atypical pathogens. *Int J Antimicrob Agents* 2001; 18:S57–S61
 - 53 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; 101:508–515
 - 54 Ruiz-Gonzalez A, Falguera M, Nogues A, et al. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown aetiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *Am J Med* 1999; 106:385–390
 - 55 Chanock RM. Mycoplasma infections of man. *N Engl J Med* 1965; 273:1199–1206
 - 56 Bochud PY, Moser F, Erard P, et al. Community-acquired pneumonia: a prospective outpatient study. *Medicine* 2001; 80:75–87
 - 57 Falguera M, Sacristan O, Nogues A, et al. Nonsevere community-acquired pneumonia: correlation between cause and severity or comorbidity. *Arch Intern Med* 2001; 161:1866–1872
 - 58 Lim WS, Macfarlane JT, Boswell TCJ, et al. SCAPA-study of community-acquired pneumonia aetiology in the UK: interim results. *Eur Respir J* 2000; 16(suppl):551S–552S
 - 59 Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med* 1995; 152:1309–1315
 - 60 Mundy LM, Oldach D, Auwaerter PG, et al. Implications for macrolide treatment in community-acquired pneumonia. *Chest* 1998; 113:1201–1206
 - 61 Plouffe JF. Importance of atypical pathogens. *Clin Infect Dis* 2000; 31(suppl):S35–S39
 - 62 File TM, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother* 1997; 41:1965–1972
 - 63 Vergis N, Akbas E, Yu VL. Legionella as a cause of severe pneumonia. *Semin Respir Crit Care Med* 2000; 21:295–304
 - 64 Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997; 337:682–687
 - 65 Chan ED, Walsh CH. Fulminant *Mycoplasma pneumoniae* pneumonia. *West J Med* 1995; 162:133–142
 - 66 Kuo CC, Jackson LA, Campbell LA, et al. *Chlamydia pneumoniae* (TWAR). *Clin Microbiol Rev* 1995; 8:451–461
 - 67 Cosentini R, Blasi F, Raccanelli R, et al. Severe community-acquired pneumonia: a possible role for *Chlamydia pneumoniae*. *Respiration* 1996; 63:61–65
 - 68 Niederman MS. Treatment of respiratory infections with quinolones. In: Andriole V, ed. *The quinolones*. 2nd ed. San Diego, CA: McGraw-Hill, 1998; 229–250

- 69 Chen D, McGeer A, de Azavedo JC, et al. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N Engl J Med* 1999; 341:233–239
- 70 Ho PL, Yung RWH, Tsang DNC, et al. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a Hong Kong multicentre study in 2000. *J Antimicrob Chemother* 2001; 48:659–665
- 71 Ho PL, Tse WQS, Kwok TK, et al. Risk factors for acquisition of Levofloxacin-resistant *Streptococcus pneumoniae*: a case-control study. *Clin Infect Dis* 2001; 32:701–707
- 72 Perez-Trallero E, Garcia-Arenzana JM, Jimenez JA, et al. Therapeutic failure and selection of resistance to quinolones in a case of pneumococcal pneumonia treated with ciprofloxacin. *Eur J Clin Microbiol Infect Dis* 1990; 9:905–906
- 73 Empey PE, Jennings HR, Thornton AC, et al. Levofloxacin failure in a patient with pneumococcal pneumonia. *Ann Pharmacother* 2001; 35:687–689
- 74 Kays NB, Smith DW. Levofloxacin treatment failure in a patient with fluoroquinolone resistant *Streptococcus pneumoniae* pneumonia. *Pharmacotherapy* 2002; 22:395–399
- 75 Campbell GD Jr, Silberman R. Drug-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 1998; 26:1185–1195