Management of Community-Acquired Respiratory Tract Infections in an Era of Increasing Antibiotic Resistance

John A. Sbarbaro, MD, MPH, David P. Nicolau, PharmD, and Carl Asche, PhD

ABSTRACT

Community-acquired respiratory tract infections (RTIs) are prevalent conditions in the U.S. and represent a major burden in health care. This article provides an overview of empirical antibiotic treatment options for patients with community-acquired RTIs, including newer classes of agents, such as the respiratory fluoroquinolones and the ketolides. We also discuss the clinical and economic utility of these agents in the current era of high levels of antibiotic resistance.

Key Words: antibiotic resistance, clinical impact, empirical prescribing

INTRODUCTION

In the U.S., community-acquired respiratory tract infections (RTIs), including acute bacterial sinusitis (ABS), community-acquired pneumonia (CAP), and acute exacerbations of chronic bronchitis (AECB), are prevalent conditions and constitute a substantial socioeconomic burden. Indeed, infections of the lower respiratory tract (i.e., CAP and AECB) represent a particular public health concern because of the morbidity and mortality associated with these infections.[1–3]

The treatment of outpatient community-acquired RTIs is usually empirical, because the causative pathogen is rarely identified before the initiation of antibiotic therapy. Antibiotic therapies recommended by current treatment guidelines[4–6] are therefore aimed at eradicating the key common causative pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antibiotic coverage of atypical organisms, such as *Mycoplasma pneumoniae, Chlamydophila (Chlamydia) pneumoniae*, and *Legionella pneumophila* (which is associated with significant morbidity and mortality), is also recommended, particularly in CAP and, to a lesser degree, in AECB.

The development and spread of antibiotic resistance among respiratory pathogens, particularly *S. pneumoniae*, now represent a key challenge in the management of RTIs. For example, high levels of pneumococcal resistance to macrolide antibiotics have led to concerns over the continued clinical efficacy of these agents.[7–9] Although increased concentrations of antibiotics may be able to overcome the effects of such resistance *in vitro*, the bioavailability and tolerability characteristics of current oral therapies generally prevent the use of higher doses of these agents in the outpatient setting. Furthermore, the intravenous (IV) route provides a means of administering high-dose antibiotics to hospitalized patients, but the costs associated with IV therapy have resulted in a preference for moving patients to oral therapy as soon as they are clinically stable.[10] Such factors highlight the need for new oral antibiotics with activity against key respiratory pathogens, in particular, strains of *S. pneumoniae* resistant to currently available agents.

In this article, we review the extent of the resistance problem in the U.S., assess the clinical and economic implications of such resistance, and provide an overview of the key characteristics of antibiotics currently available for the empirical treatment of outpatients with community-acquired RTIs, including newer classes of agents such as the respiratory fluoroquinolones and ketolides.

ANTIBIOTIC RESISTANCE

Resistance Trends

Surveillance studies conducted in the U.S. over the last decade have revealed significant levels of *in vitro* resistance to beta-lactams among all major respiratory pathogens.[11–15] Approximately 30% of *S. pneumoniae* isolates are nonsusceptible to penicillin, and a similar proportion of *H. influenzae* isolates produce beta-lactamase, which mediates resistance to ampicillin (Principen, Apothecon), amoxicillin (e.g., Amoxil, GlaxoSmithKline), and certain cephalosporins.

With *S. pneumoniae*, resistance to macrolides currently affects approximately 30% of isolates collected in the U.S.[11,13,14,16] Modification of the drug target site and active efflux of the drug from the cell are the two main mechanisms of pneumococcal macrolide resistance. The most common form of target-site modification results from the presence of the *erm*(B) gene, which encodes an enzyme that methylates bacterial ribosomal RNA, whereas macrolide efflux from bacteria is mediated by the product of the *mef*(A) gene.

Historically, the *mef*(A) genotype has been associated with low-to-moderate levels of macrolide resistance, characterized by minimum inhibitory concentration (MIC) ranges of 1 to 16 mcg/ml); *erm*(B)-mediated resistance has been associated with higher-level resistance (MIC ranges of 64 mcg/ml or

Dr Sbarbaro is Professor of Medicine and Preventive Medicine at the University of Colorado Health Sciences Center in Denver, Colorado. Dr Nicolau is Director of the Center for Anti-infective Research and Development at Hartford Hospital in Hartford, Connecticut. Dr Asche is Research Associate Professor at the Outcomes Research Center in the Department of Pharmacotherapy, College of Pharmacy, at the University of Utah in Salt Lake City, Utah.

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greater). However, results from the PROTEKT US (*P*rospective *R*esistant *O*rganism *T*racking and *E*pidemiology for the *K*etolide *T*elithromycin in the *US*) surveillance study have demonstrated an increase in macrolide MICs among *mef*(A)-positive *S. pneumoniae* isolates (range, from 1 to more than 256 mcg/ml).[17] These results suggest that *mef*(A)-positive pneumococcal strains can no longer necessarily be regarded as displaying low-level resistance to macrolides.

Data collected over four years of the PROTEKT US study (from 2000–2001 to 2003–2004) have confirmed that in the U.S., the *mef*(A)-mediated mechanism of macrolide resistance predominates among *S. pneumoniae* clinical isolates.[16] However, the prevalence of *mef*(A) in macrolide-resistant isolates decreased from 68.8% in 2000–2001 to 62.3% in 2003–2004, whereas a concomitant increase in the proportions of isolates positive for both *erm*(B) and *mef*(A) occurred (from 9.7% in 2000–2001 to 18.4% in 2003–2004).[16]

Of note, almost all *S. pneumoniae* isolates with this dual mechanism of resistance were shown to be multidrug-resistant and displayed high-level resistance to a range of antibiotics, including penicillin, amoxicillin, tetracycline, clindamycin (Cleocin, Pfizer), and trimethoprim–sulfamethoxazole (Bactrim, Women First).

Factors Contributing to the Development of Resistance, Carriage, and Spread

The inappropriate use of antibiotics, for example, in treating viral upper RTIs, has been identified as a major contributor to the development and spread of antibiotic resistance among respiratory pathogens. Analyses of data from national and international surveillance studies have indicated a link between increased macrolide consumption and increased rates of pneumococcal resistance to this class of antibiotics.[18–21]

The use of broad-spectrum drugs (i.e., agents with activity extending beyond the common respiratory pathogens) may also increase the risk of resistance in nonrespiratory gram-negative bacteria, such as normal gastrointestinal flora. For example, the increased use of the fluoroquinolones has been associated with the emergence of resistance among gram-negative bacilli in the gastrointestinal flora, including clinically important pathogens such as *Pseudomonas aeruginosa, Enterobacter agglomerans,* and *Escherichia coli*.[22,23]

Differences in the pharmacokinetic and pharmacodynamic properties of antibiotics may also influence the development of resistance in bacterial pathogens. Antibiotics, such as the macrolides, with a bacteriostatic mode of activity, have a greater potential to select for resistance than agents with bactericidal activity, such as penicillins, fluoroquinolones, and ketolides.[24–26] The half-life of a drug can also contribute to the selection of resistance: agents with long elimination half-lives result in prolonged exposure of bacteria to sub-inhibitory concentrations of the drug, compared with agents with shorter half-lives.

A study conducted by Kastner and Guggenbichler in 2001[25] compared the promotion of resistance in the oral flora of children treated with one of two macrolide antibiotics (azithromycin and clarithromycin), with half-lives of 60 to 70 hours and three to seven hours, respectively. Six weeks after treatment, only 33% of the patients receiving clarithromycin (e.g., Biaxin, Abbott) had macrolide-resistant isolates, compared with 87% of the patients receiving azithromycin (Zithromax, Pfizer).

Adequate drug concentrations at the site of infection are also important to prevent the development of resistant strains.[26] Azithromycin achieves low concentrations in lung epithelium-lining fluid, compared with other macrolides.[27] This not only limits its clinical utility in terms of current macrolide resistance rates; it also has important implications for the further selection of resistance.

Various patient-related risk factors are also associated with an increased risk of carriage and spread of antibiotic-resistant bacterial strains. Patients identified as being particularly at risk include the young (younger than five years of age), the elderly (older than 65 years of age), those with coexisting illness or underlying disease, and patients with immunodeficiency or human immunodeficiency virus (HIV) infection. Clonal dissemination of drug-resistant strains of bacteria may occur in children attending day care centers or in family members of a child attending day care. Among adults, rates of carriage of drug-resistant strains are highest among those who are institutionalized in hospitals, jails, and nursing homes.[28]

Prior antibiotic use (i.e., within the three months preceding treatment) has been identified as an important predictor of infection with drug-resistant bacterial strains. A Canadian analysis of data from 3,339 patients with invasive pneumococcal infections[29] demonstrated that the single most important risk factor for resistance to beta-lactams, macrolides, fluoroquinolones, or trimethoprim–sulfamethoxazole was the previous use of an agent from the same class. Of note, in addition to being a major risk factor for infection with macrolide-resistant *S. pneumoniae*, prior azithromycin therapy was also associated with an increased risk of infection with strains resistant to penicillin or trimethoprim–sulfamethoxazole. The results also demonstrated that infection with fluoroquinolone-resistant pneumococci was associated with residing in a nursing home and in acquiring pneumococcal infection in a hospital.[29]

Clinical and Economic Effects of Resistance

The clinical impact of *in vitro* antibiotic resistance has been difficult to assess, given that most community-acquired RTIs are treated in the outpatient setting, in which microbiological data are rarely collected before treatment is begun. The most compelling evidence to date surrounds the possible association between macrolide resistance and adverse clinical outcomes. Reviews of the published literature[9,30] have described a number of cases of empirical macrolide treatment failure (resulting in hospitalization of patients with breakthrough bacteremia) that were associated with infection by macrolide-resistant strains of *S. pneumoniae*.

Rzeszutek et al.[30] reviewed cases of macrolide treatment failure published between 1990 and 2002. Of the 33 cases listed, 31 involved patients who had received macrolides as outpatients and who had required hospitalization as a result of therapy failure. The other two cases involved previously healthy hospitalized patients who did not respond to intravenous (IV) macrolide therapy and who subsequently died after their clinical condition deteriorated. In both of these cases, macrolide-resistant *S. pneumoniae* were isolated from blood cultures taken during macrolide therapy.

Further evidence supporting a link between macrolide

resistance and adverse clinical outcomes emerged from case-control studies of hospitalized patients with breakthrough bacteremia. Two such studies showed that treatment failure occurred more frequently in patients infected with a macrolide-resistant *S. pneumoniae* strain than in those infected with a macrolide-susceptible strain.[31,32] Although the clearest evidence of an association between macrolide treatment failure and macrolide resistance has come from studies of patients hospitalized with breakthrough bacteremia, the true incidence of macrolide treatment failure is probably much higher than that suggested by the case reports and observational studies published to date. Again, this is a result of the lack of microbiological testing in the outpatient setting. It is in this setting where most patients receiving macrolides are treated.

Most evidence to date applies to the clinical use of macrolides; however, failure of empirical treatment with levofloxacin attributable to fluoroquinolone resistance has also been reported in patients with pneumococcal RTIs,[33] and infection with penicillin-resistant *S. pneumoniae* has been reported to lead to an increased risk of suppurative complications.[34]

Clinical treatment failures contribute to substantial health care expenditure associated with RTIs. Direct costs of treatment failure include those associated with additional prescriptions, extra tests and procedures, and hospitalizations; indirect costs may be incurred by patients experiencing increased disability and loss of productivity.[3,35]

Klepser and colleagues assessed the economic impact of infection with penicillin-nonsusceptible strains of *S. pneumoniae* in a study of hospitalized patients.[36] The results from this analysis indicated that infection with a nonsusceptible isolate was associated with significantly higher costs (total, $10,309; room, $3,771; and nursing, $3,859) than infection with a susceptible isolate (total, $7,802; room, $2,829; and nursing, $2,886).

ANTIBIOTIC TREATMENT OPTIONS

The association between antibiotic use, increasing rates of resistance, and clinical treatment failure underlines the importance of optimizing antibiotic use in patients with community-acquired RTIs. Table 1 summarizes the key attributes to consider in selecting an antibiotic for empirical treatment; these include (1) the spectrum of activity, (2) the potential of the antibiotic to induce and select for resistance, (3) the tolerability and convenience of the regimen, and (4) the antibiotic's impact on health outcomes.

Treatment Guidelines and Recommendations

Selecting the initial antibiotic therapy is generally considered central to achieving bacterial eradication and clinical success in patients with community-acquired RTIs. Treatment guidelines have been developed by a number of North American professional organizations aimed at promoting the use of appropriate antibiotic therapy[1,4–6,37,38] while minimizing the development and spread of resistance.

A number of guidelines recommend that patients be classified on the basis of the severity of disease and the presence or absence of risk factors for infection with drug-resistant bacteria prior to the selection of initial antibiotic therapy. Historically, guidelines have focused primarily on providing coverage against the key common respiratory tract pathogens: *S. pneumoniae, H. influenzae,* and *M. catarrhalis.* In the primary care setting, where causative pathogens are rarely identified before treatment, beta-lactams or macrolides are typically recommended as initial empirical therapy for AECB and ABS.[6,38] Macrolides, unlike the beta-lactams, also cover atypical pathogens, including *C. pneumoniae, M. pneumoniae*, and *L. pneumophila,* and are therefore preferred for the empirical treatment of CAP.[1,4,5,37]

More recently, the prevalence of *in vitro* resistance to beta-lactam and macrolide antibiotics, in addition to concerns about the clinical and economic impact of treatment failure associated with such resistance, has led to the development of alternative oral antibiotics for community-acquired RTIs, including the fluoroquinolones and ketolides.

Second- and third-generation fluoroquinolones, such as levofloxacin (Levaquin, Ortho-McNeil), gatifloxacin (Tequin, Bristol-Myers Squibb), moxifloxacin (Avelox, Bayer), and gemifloxacin mesylate (Factive, GeneSoft), provide coverage against

Table 1 Ideal Characteristics of an Antibiotic Agent for the Treatment of Acute Community-Acquired Respiratory Tract Infections

Parameter	Ideal Property
Antibacterial spectrum	Coverage against: • Key common respiratory pathogens ◦ *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* • Penicillin-resistant and macrolide-resistant strains of *Streptococcus pneumoniae* • Atypical or intracellular pathogens ◦ *Mycoplasma pneumoniae, Chlamydophila (Chlamydia) pneumoniae, Legionella pneumophila* Minimal impact on: • Gram-negative nonrespiratory bacterial flora and pathogens
Tolerability and convenience	• Available as a short course of oral therapy • Acceptable tolerability profile
Health outcome	• Favorable impact on additional utilization of health care resources • Reduction in overall costs of care

all typical and atypical respiratory pathogens, and they display good tissue penetration, particularly in the respiratory tract.[39] In clinical trials, these agents have been as effective as standard comparator antibiotics (including beta-lactams and macrolides) for patients with community-acquired RTIs.[40–43]

However, because these agents also display *in vitro* activity against gram-negative bacteria, there is concern that their use may result in the development of resistance in important nonrespiratory bacterial flora and pathogens, a concept known as "collateral damage." Indeed, reports have documented increased rates of fluoroquinolone resistance among gram-negative pathogens (including *E. coli*, *Enterobacter* spp., *Pseudomonas* spp., and *Klebsiella* spp.) linked to the increased prescription of these agents for a range of infections.[23,44,45] Moreover, this is of increasing concern in the community-acquired RTI patient population, because it is clear that over the past several years, the use of both the macrolides and beta-lactams has declined in patients with CAP, whereas the use of fluoroquinolones continues to escalate.[46] Given this potential for collateral damage, RTI treatment guidelines generally recommend that the fluoroquinolones be reserved for specific patient groups, including those who have not responded to treatment with other antibiotics and patients with severe disease or multiple risk factors for comorbidity.

Another option for outpatient treatment of community-acquired RTIs is the ketolide antibiotic telithromycin (Ketek, Aventis), which the U.S. Food and Drug Administration (FDA) approved in 2004 for clinical use in treating outpatients (18 years of age or older) with ABS, AECB, and CAP of mild-to-moderate severity.

Telithromycin provides a tailored spectrum of activity against key common and atypical pathogens. Unlike the fluoroquinolones and beta-lactams, however, it displays minimal activity against gram-negative nonrespiratory pathogens and commensal bacteria.[47] Furthermore, *in vitro* data indicate that this agent has a low potential to select for resistance among respiratory pathogens.[48,49] These *in vitro* characteristics, combined with its high penetration into bronchopulmonary sites of infection[50,51] and an efficacy profile equivalent to that of standard comparator agents (including macrolides, beta-lactams, and fluoroquinolones) in patients with community-acquired RTIs,[52] suggest that telithromycin will become a useful therapeutic option. One study of patients with CAP found that telithromycin achieved significantly superior rates of clinical cure than rates achieved with other usual-care antibiotics (including beta-lactams, macrolides, and fluoroquinolones).[53]

Tolerability and Convenience

Patients' nonadherence to antibiotic regimens, resulting in subtherapeutic drug concentrations in target tissues, leads to an increased risk of treatment failure and may increase selection pressure for the development of antibiotic resistance among respiratory pathogens. Adherence to therapy is influenced by several factors, including drug tolerability and the convenience of the dosing regimen.

Differing tolerability profiles, both between and within antibiotic classes, may affect adherence to therapy, and clinicians should therefore consider this fact when selecting empirical antibiotic therapy. Compliance seems to be greatest with convenient, once-daily regimens of short duration.[54] As a result, most of the newer-generation oral antibiotics introduced for the treatment of community-acquired RTIs have short, once-daily or twice-daily dosing regimens. For example, azithromycin and telithromycin offer once-daily dosing, but amoxicillin and amoxicillin–clavulanate (Augmentin, GlaxoSmithKline) must be administered twice and three times daily, respectively.

Health Outcomes

Until recently, most clinical studies focused primarily on the clinical and bacteriological efficacy of antibiotics in the treatment of RTIs; they were not designed to capture specific differences in outcomes between agents (e.g., speed of recovery or time to symptom resolution, utilization of health care resources, and quality-of-life measures). However, studies of the newer classes of antibiotic agents, including the fluoroquinolones and the ketolides, have begun to address these issues, particularly in patients with infections of the lower respiratory tract (CAP and AECB).

Acute Exacerbations of Chronic Bronchitis

In a study of patients with AECB, Wilson and colleagues[55] showed that significantly fewer patients receiving the fluoroquinolone moxifloxacin (9.5%) required additional antibiotic treatment, compared with patients who received clarithromycin (15.1%). In addition, the time to the next exacerbation was longer with moxifloxacin (median, 131 days) than with clarithromycin (median, 103.5 days).

Similar results were also noted in a study comparing gemifloxacin and clarithromycin for AECB. Significantly more patients who had received gemifloxacin remained recurrence-free 26 weeks after treatment (71%) than those who were treated with clarithromycin (58.5%).[56]

A trial designed to compare the efficacy and tolerability of telithromycin and clarithromycin in patients with AECB has also documented patients' utilization of health care resources, including the following:[57]

- The proportion of patients making unscheduled AECB-related visits to the emergency department was lower for those taking telithromycin (0%) than clarithromycin (2.8%).
- Fewer telithromycin-treated patients were hospitalized because of AECB (0.4% vs. 1.4%, respectively).
- Fewer telithromycin patients reported days lost from work (23% vs. 31%, respectively).[57]

It is estimated that these differences in health care resource utilization contributed to a direct cost savings of approximately $146 per patient.

In another study,[58] telithromycin therapy resulted in fewer hospitalizations and days spent in hospital than treatment with amoxicillin–clavulanate (when the dose was 500/125 mg three times daily for 10 days).

Community-Acquired Pneumonia

As in AECB, relatively few studies investigating the efficacy of oral antibiotic therapies for patients with mild-to-moderate CAP treated on an outpatient basis have included measures of health care resource utilization.

Among the fluoroquinolones, outcome differences between moxifloxacin and a standard oral therapy selected by the investigator (amoxicillin and clarithromycin, either alone or in combination) were assessed as part of a study conducted by Torres et al.[59] Analyses of data, including the use of additional antibiotics, hospitalizations, work status, and quality of life, indicated no significant differences between the two treatment arms. In contrast, an economic evaluation based on the use of resources concluded that levofloxacin was less costly than cefuroxime axetil (Ceftin, GlaxoSmithKline) for outpatients with CAP; levofloxacin was associated with a total cost savings of $169 per patient.[60]

CAP-associated data on health care resource utilization were collected in two studies involving patients receiving telithromycin or clarithromycin. Given that hospitalization is recognized as the major cost component in the treatment of patients with CAP,[2] data from these two studies were pooled to allow further analysis of differences in hospital-associated costs between the treatment groups.[61] Although the two treatments showed equivalent clinical efficacy, telithromycin (for five, seven, or 10 days) was associated with significantly fewer CAP-related hospitalizations (1.2 vs. 3.6 per 100 patients, respectively) and CAP-related days spent in hospital (8.8 vs. 33.8 days per 100 patients, respectively), resulting in an estimated cost savings of $302 per patient.

In summary, these investigations suggest that some of the newer antibiotic treatment options, including the fluoroquinolones and telithromycin, may offer significant health care and economic benefits in patients with community-acquired RTIs.

CONCLUSION

Although antibiotic resistance represents a major challenge in the management of community-acquired RTIs and affects both clinical and economic outcomes, the appropriate use of antibiotics is considered essential to addressing this problem. Health care providers are now advised to consider several factors when they prescribe oral antibiotic therapy, including:

- the use of an agent with a tailored spectrum of activity.
- correct dosing and duration of treatment.
- local antibiotic resistance patterns.
- patient risk factors for infection with resistant pathogens, especially when patients have previously used antibiotics.

These considerations, which are aimed at minimizing both the risk of treatment failure and the development of future resistance, may also reduce patients' utilization of health care resources and costs associated with the treatment of community-acquired RTIs.

REFERENCES

1. Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000;31:347–382.
2. Niederman MS, McCombs JS, Unger AN, et al. The cost of treating community-acquired pneumonia. *Clin Ther* 1998;20:820–837.
3. Niederman MS, McCombs JS, Unger AN, et al. Treatment cost of acute exacerbations of chronic bronchitis. *Clin Ther* 1999;21:576–591.
4. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;163:1730–1754.
5. 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;37:1405–1433.
6. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2004;130:1–45.
7. Jacobs MR. *In vivo veritas*: *In vitro* macrolide resistance in systemic *Streptococcus pneumoniae* infections does result in clinical failure. *Clin Infect Dis* 2002;35:565–569.
8. Lonks JR, Garau J, Medeiros AA. Implications of antimicrobial resistance in the empirical treatment of community-acquired respiratory tract infections: The case of macrolides. *J Antimicrob Chemother* 2002;50 (Suppl S2):87–92.
9. Klugman KP, Lonks JR. Hidden epidemic of macrolide-resistant pneumococci. *Emerg Infect Dis* 2005;11:802–807.
10. Kuti JL, Capitano B, Nicolau DP Cost-effective approaches to the treatment of community-acquired pneumonia in the era of resistance. *Pharmacoeconomics* 2002;20:513–528.
11. Doern GV, Pfaller MA, Kugler K, et al. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clin Infect Dis* 1998;27:764–770.
12. Hoban D, Waites K, Felmingham D. Antimicrobial susceptibility of community-acquired respiratory tract pathogens in North America in 1999–2000: Findings of the PROTEKT surveillance study. *Diagn Microbiol Infect Dis* 2003;45:251–259.
13. Brown SD, Rybak MJ. Antimicrobial susceptibility of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus influenzae* collected from patients across the USA, in 2001–2002, as part of the PROTEKT US study. *J Antimicrob Chemother* 2004;54(Suppl S1):i7–i15.
14. Jacobs MR, Bajaksouzian S, Windau A, et al. Susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* to 17 oral antimicrobial agents based on pharmacodynamic parameters: 1998–2001 U.S. Surveillance Study. *Clin Lab Med* 2004;24:503–530.
15. Low DE, Felmingham D, Brown SD, et al. Activity of telithromycin against key pathogens associated with community-acquired respiratory tract infections. *J Infect* 2004;49:115–125.
16. Farrell DJ, Brown SD, Traczewski MM, et al. Change in distribution of macrolide-resistant *Streptococcus pneumoniae* genotypes over 4 years: Data from PROTEKT US 2000–2004. Presented at the 105th General Meeting of the American Society for Microbiology (Abstract A-100), June 5–9, 2005, Atlanta, GA.
17. Farrell DJ, Jenkins SG. Distribution across the USA of macrolide resistance and macrolide resistance mechanisms among *Streptococcus pneumoniae* isolates collected from patients with respiratory tract infections: PROTEKT US 2001–2002. *J Antimicrob Chemother* 2004;54(Suppl 1):i17–i22.
18. Granizo JJ, Aguilar L, Casal J, et al. *Streptococcus pneumoniae* resistance to erythromycin and penicillin in relation to macrolide and β-lactam consumption in Spain (1979–1997). *J Antimicrob Chemother* 2000;46:767–773.
19. Pihlajamaki M, Kotilainen P, Kaurila T, et al. Macrolide-resistant *Streptococcus pneumoniae* and use of antimicrobial agents. *Clin Infect Dis* 2001;33:483–488.
20. Boccia D, Alegiani SS, Pantosti A, et al. The geographic relationship between the use of antimicrobial drugs and the pattern of resistance for *Streptococcus pneumoniae* in Italy. *Eur J Clin Pharmacol* 2004;60:115–119.
21. Dias R, Caniça M. Emergence of invasive erythromycin-resistant *Streptococcus pneumoniae* strains in Portugal: Contribution and phylogenetic relatedness of serotype 14. *J Antimicrob Chemother* 2004;54:1035–1039.
22. Richard P, Delangle MH, Raffi F, et al. Impact of fluoroquinolone administration on the emergence of fluoroquinolone-resistant

gram-negative bacilli from gastrointestinal flora. *Clin Infect Dis* 2001;32:162–166.
23. Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in U.S. intensive care units: Implications for fluoroquinolone use. *JAMA* 2003;289:885–888.
24. Stratton CW. Dead bugs don't mutate: Susceptibility issues in the emergence of bacterial resistance. *Emerg Infect Dis* 2003;9:10–16.
25. Kastner U, Guggenbichler JP Influence of macrolide antibiotics on promotion of resistance in the oral flora of children. *Infection* 2001;29:251–256.
26. Nicolau DP Treatment with appropriate antibiotic therapy in community-acquired respiratory tract infections. *Am J Manag Care* 2004;10(Suppl):S381–S388.
27. Patel KB, Xuan D, Tessier PR, et al. Comparison of bronchopulmonary pharmacokinetics of clarithromycin and azithromycin. *Antimicrob Agents Chemother* 1996;40:2375–2379.
28. Campbell GD Jr, Silberman R. Drug-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 1998;26:1188–1195.
29. Vanderkooi OG, Low DE, Green K, et al., for the Toronto Invasive Bacterial Disease Network. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis* 2005;40: 1288–1297.
30. Rzeszutek M, Wierzbowski A, Hoban DJ, et al. A review of clinical failures associated with macrolide-resistant *Streptococcus pneumoniae*. *Int J Antimicrob Agents* 2004;24:95–104.
31. 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.
32. van Kerkhoven D, Peetermans WE, Verbist L, Verhaegen J. Breakthrough pneumococcal bacteraemia in patients treated with clarithromycin or oral beta-lactams. *J Antimicrob Chemother* 2003; 51:691–696.
33. Fuller JD, Low DE. A review of *Streptococcus pneumoniae* infection treatment failures associated with fluoroquinolone resistance. *Clin Infect Dis* 2005;41:118–121.
34. Einarsson S, Kristjansson M, Kristinsson KG, et al. Pneumonia caused by penicillin-nonsusceptible and penicillin-susceptible pneumococci in adults: A case-control study. *Scand J Infect Dis* 1998;30:253–256.
35. Colice GL, Morley MA, Asche C, Birnbaum HG. Treatment costs of community-acquired pneumonia in an employed population. *Chest* 2004;125:2140–2145.
36. Klepser ME, Klepser DG, Ernst EJ, et al. Health care resource utilization associated with treatment of penicillin-susceptible and -nonsusceptible isolates of *Streptococcus pneumoniae*. *Pharmacotherapy* 2003;23:349–359.
37. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: A report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Arch Intern Med* 2000; 160:1399–1408.
38. Balter MS, La Forge J, Low DE, et al. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can Respir J* 2003;10(Suppl B):3B–32B.
39. Wise R, Honeybourne D. Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract. *Eur Respir J* 1999;14:221–229.
40. Bhavnani SM, Andes DR. Gemifloxacin for the treatment of respiratory tract infections: *In vitro* susceptibility, pharmacokinetics and pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2005;25:717–740.
41. Hurst M, Lamb HM, Scott LJ, Figgitt DP. Levofloxacin: An updated review of its use in the treatment of bacterial infections. *Drugs* 2002;62:2127–2167.
42. Miravitlles M. Moxifloxacin in respiratory tract infections. *Expert Opin Pharmacother* 2005;6:283–293.
43. Sethi S. Gatifloxacin in community-acquired respiratory tract infection. *Expert Opin Pharmacother* 2003;4:1847–1855.
44. Goettsch W, van Pelt W, Nagelkerke N, et al. Increasing resistance to fluoroquinolones in *Escherichia coli* from urinary tract infections in the Netherlands. *J Antimicrob Chemother* 2000; 46:223–228.
45. Livermore DM, James D, Reacher M, et al. Trends in fluoroquinolone (ciprofloxacin) resistance in *Enterobacteriaceae* from bacteremias, England and Wales, 1990–1999. *Emerg Infect Dis* 2002;8:473–478.
46. MacDougall C, Guglielmo BJ, Maselli J, Gonzales R. Antimicrobial drug prescribing for pneumonia in ambulatory care. *Emerg Infect Dis* 2005;11:380–384.
47. Felmingham D, Farrell DJ. *In vitro* activity of telithromycin against gram-negative bacterial pathogens. *J Infect* 2005 (Epub ahead of print).
48. Davies TA, Dewasse BE, Jacobs MR, Appelbaum PC. *In vitro* development of resistance to telithromycin (HMR 3647), four macrolides, clindamycin, and pristinamycin in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2000;44:414–417.
49. Reinert RR, Felmingham D, and the EU PROTEKT Study Group. Sustained antimicrobial activity of telithromycin in Europe post-launch: The PROTEKT study (years 1–4). Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Abstract C2-813), October 30–November 2, 2004, Washington, DC, and the American Society for Microbiology, 2004.
50. Muller-Serieys C, Soler P, Cantalloube C, et al. Bronchopulmonary disposition of the ketolide telithromycin (HMR 3647). *Antimicrob Agents Chemother* 2001;45:3104–3108.
51. Ong CT, Dandeker P, Sutherland C, et al. Intrapulmonary concentrations of telithromycin: Clinical implications against *Streptococcus pneumoniae*. *Chemotherapy* 2005;51:339–346.
52. Carbon C. A pooled analysis of telithromycin in the treatment of community-acquired respiratory tract infections in adults. *Infection* 2003;31:308–317.
53. Mouton Y, Thamlikitkul V, Nieman RB, Janus C. Telithromycin versus other first-line single-agent antibiotics in the treatment of community-acquired pneumonia: A randomised superiority trial. Presented at the 15th European Congress of Clinical Microbiology and Infectious Diseases (Abstract P883), April 2–5, 2005, Copenhagen, Denmark.
54. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother* 2002;49: 897–903.
55. Wilson R, Allegra L, Huchon G, et al. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest* 2004; 125:953–964.
56. Wilson R, Schentag JJ, Ball P, Mandell L, for the 068 Study Group. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther* 2002;24:639–652.
57. Fogarty C, de Wet R, Mandell L, et al. Five-day telithromycin once daily is as effective as 10-day clarithromycin twice daily for the treatment of acute exacerbations of chronic bronchitis and is associated with reduced healthcare resource utilization. *Chest* 2005;128:1980–1988.
58. Chang JR, Stewart J, Cadilhac M, et al. Telithromycin (TEL) results in fewer hospitalizations than amoxicillin–clavulanate (AMC) in the outpatient treatment of acute exacerbations of chronic bronchitis (AECB). Presented at the annual meeting of the International Society of Pharmacoeconomics and Outcomes Research (Abstract PIN2), May 18–21, 2003, Arlington, VA.
59. Torres A, Muir JF, Corris P, et al. Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia. *Eur Respir J* 2003;21:135–143.
60. Rittenhouse BE, Stinnett AA, Dulisse B, et al. An economic evaluation of levofloxacin versus cefuroxime axetil in the outpatient treatment of adults with community-acquired pneumonia. *Am J Manag Care* 2000;6:381–389.
61. Niederman MS, Chang JR, Stewart J, et al. Hospitalization rates among patients with community-acquired pneumonia treated with telithromycin vs clarithromycin: Results from two randomized, double-blind, clinical trials. *Curr Med Res Opin* 2004;20: 969–980. ■