Use of the Respiratory Fluoroquinolones for the Outpatient Management of Community-Acquired Pneumonia

Hans H. Liu, MD

Jefferson Medical College, Philadelphia, Pennsylvania, and Bryn Mawr Medical Specialists Association, Bryn Mawr, Pennsylvania

ABSTRACT

Background: Approximately 4 million cases of community-acquired pneumonia (CAP) occur in the United States each year, with the majority treated on an outpatient basis. The first fluoroquinolones (eg, ciprofloxacin) were used with caution for respiratory tract infections due to limited in vitro activity against common gram-positive pathogens. With the availability of levofloxacin, followed by gatifloxacin and moxifloxacin hydrochloride, which exhibited increased activity against gram-positive organisms, the fluoroquinolones have become a practical choice for the treatment of CAP.

Objective: The aim of this review was to compare the respiratory fluoroquinolones in the outpatient management of CAP.

Methods: We conducted a search for English-language articles (key terms: *fluoroquinolone*, *levofloxacin*, *gatifloxacin*, *moxifloxacin*, and *pneumonia*; years: 1996–2004). Data from published literature were reviewed regarding clinical and microbiologic efficacy and tolerability; pharmacokinetic and pharmacodynamic properties; and drug costs of levofloxacin, gatifloxacin, and moxifloxacin.

Results: The 3 fluoroquinolones reviewed showed comparable clinical and microbiologic efficacy for the treatment of CAP. In general, the fluoroquinolones were well tolerated, although some differences have been reported, including higher rates of gastrointestinal and other adverse events for gatifloxacin and moxifloxacin. Gatifloxacin and moxifloxacin exhibited greater in vitro potency than levofloxacin against *Streptococcus pneumoniae*. However, levofloxacin achieved a higher serum drug concentration than the other agents, allowing similar attainment of pharmacokinetic and pharmacodynamic targets required for effective treatment.

Conclusions: The respiratory fluoroquinolones provided appropriate first-line treatment in select patients with CAP on the basis of their microbiologic

Accepted for publication May 18, 2004.

Reproduction in whole or part is not permitted.

0011-393X/04/\$19.00

and clinical efficacy and their safety profiles. (*Curr Ther Res Clin Exp.* 2004;65: 225–238) Copyright © 2004 Excerpta Medica, Inc.

Key words: community-acquired pneumonia, fluoroquinolones, clinical efficacy, safety.

INTRODUCTION

Approximately 4 million cases of community-acquired pneumonia (CAP) occur in the United States each year, with the majority treated on an outpatient basis.¹ Although upper respiratory tract infections (RTIs) are commonly viral and may not require a specific therapy, antibacterial therapy is usually indicated for CAP because of the risk for serious complications (eg, bacteremia and meningitis) if bacterial infection is left untreated. Chest radiography is recommended to confirm the diagnosis of CAP because a negative result may prevent unnecessary antimicrobial therapy.² Although microbiologic studies (Gram stain and sputum culture) might be valuable in determining optimal therapy, cost and time constraints in the primary care setting favor empiric treatment on an outpatient basis.

CAP treatment guidelines offer important criteria in deciding which patients should be initiated on fluoroquinolone therapy. In 2000, guidelines from the Infectious Diseases Society of America (IDSA)² noted that the increasing prevalence of drug-resistant and multidrug-resistant *Streptococcus pneumoniae* has complicated the empiric use of some agents, particularly the macrolides and beta-lactams. Initial empiric treatment should also provide coverage of typical and atypical pathogens. The IDSA treatment guidelines were updated in 2003³ and now recommend using a macrolide or doxycycline for previously healthy patients with no recent (within the past 3 months) antibiotic therapy. A respiratory fluoroquinolone (one with enhanced activity against *S pneumoniae*, eg, levofloxacin, gatifloxacin, or moxifloxacin) is recommended for outpatients with recent antibiotic treatment or with comorbidities (eg, chronic obstructive pulmonary disease, diabetes, renal or congestive heart failure, or malignancy). Guidelines from the American Thoracic Society⁴ recommend similar empiric treatments: a macrolide or doxycycline for patients with no cardiopulmonary disease or modifying factors, and a respiratory fluoroquinolone or a beta-lactam/macrolide combination for patients at risk for drug-resistant *S pneumoniae*, or patients with cardiopulmonary disease or other modifying factors.

The first fluoroquinolones (eg, ciprofloxacin) were used with caution for RTIs because of their limited in vitro activity against common gram-positive pathogens, particularly *S pneumoniae*. With the availability of levofloxacin, the fluoroquinolones have become a practical choice for the treatment of RTIs, including CAP. Levofloxacin possessed potent activity against typical and atypical pathogens, and improved pharmacokinetic properties allowed convenient

QD dosing. Its high bioavailability permitted equally potent IV and PO dosing that has facilitated outpatient management of CAP, decreasing hospital admissions, lengths of stay, and total health care costs. Several other fluoroquinolones have been developed but have failed to reach the US market or have been withdrawn, primarily due to safety concerns. To date, gatifloxacin and moxifloxacin have joined levofloxacin to comprise the respiratory fluoroquinolones, with gemifloxacin poised to enter the US market in the near future.

The aim of this review was to describe the role of the respiratory fluoroquinolones in the outpatient management of CAP. (Because of limited clinical experience with gemifloxacin, this agent was not included in the discussion.) These drugs provide appropriate first-line treatment in selected patients with CAP on the basis of their microbiologic and clinical efficacy and their safety profiles. A thorough understanding of each agent will assist the practicing clinician in the routine clinical use of this antimicrobial class.

METHODS

A literature search was conducted using the PubMed Database (National Library of Medicine) for English-language articles (key terms: *fluoroquinolone*, *pneumonia*, *levofloxacin*, *moxifloxacin*, and *gatifloxacin*; years: 1996–2004). Articles related to ventilator-associated pneumonia or nosocomial pneumonia were excluded. The literature was supplemented with a manual search of reference lists to identify relevant articles.

MICROBIOLOGIC ACTIVITY

CAP is caused by a variety of pathogens, with the most common being *S pneumoniae*, *Haemophilus influenzae*, and the atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp).^{5,6} Etiologic data from non-severe or outpatient CAP studies^{7,8} have continued to show not only a high prevalence of *S pneumoniae* infection in these patients, but also a greater role of atypical pathogens, especially *M pneumoniae* and *C pneumoniae*, which might account for ~30% to 40% of all CAP infections in which the cause is determined. *M pneumoniae* infection has been associated with younger patients (aged <50 years) without significant comorbidities. Older patients (aged ≥50 years) or patients with significant underlying disease are more likely to be infected with *S pneumoniae*, although atypical pathogens may have a role as predisposing factors or copathogens.⁶

Current treatment strategies must take into account the significant prevalence of atypical infections, together with increasing *S pneumoniae* resistance to several classes of antimicrobials. Certain antimicrobials, such as the beta-lactams, are ineffective against atypical pathogens because these agents cannot penetrate the host cell membrane (and thus are not effective against intracellular pathogens such as *C pneumoniae* or *Legionella pneumophila*) or are not

active against pathogens that lack a cell wall (eg, *M pneumoniae*). Resistance to penicillin, cephalosporins, and macrolides by *S pneumoniae* presents a major concern for the empiric use of these agents in treating CAP. Surveillance studies that track the resistance of respiratory pathogens in the United States can provide crucial guidance in selecting appropriate empiric therapy. Based on data from the Tracking Resistance in the US Today 6 (TRUST 6) surveillance study,⁹ which included 7671 *S pneumoniae* isolates from across the United States in 2001–2002, only 66% of isolates were susceptible to penicillin and 68% were susceptible to trimethoprim–sulfamethoxazole. Similarly, *S pneumoniae* susceptibility to the macrolides has been decreasing and is now approaching 70%.^{9–11} A greater percentage of *S pneumoniae* isolates appear to be susceptible to amoxicillin than to penicillin, although the difference might be due to penicillin-intermediate strains testing as susceptible to amoxicillin.^{10,12} Certain other beta-lactams, such as ceftriaxone and cefotaxime, continue to be effective against >90% of *S pneumoniae* strains in the United States. However, cross-resistance to various classes of antimicrobial agents, including macrolides and cephalosporins, is commonly observed with penicillin-resistant isolates (**Table I**).¹² The correlation between bacterial resistance and clinical failure remains controversial^{13,14} and requires further research to fully understand the clinical significance.

Although the fluoroquinolones have been used extensively for several years, *S pneumoniae* resistance remains rare and sporadic in the United States. Surveillance data^{9–11} show that ≥99% of *S pneumoniae* isolates were susceptible to the respiratory fluoroquinolones, and annual reports from TRUST⁹ have indicated that the minimum inhibitory concentration (MIC) for 90% of isolates (MIC₉₀) has not increased in recent years. Fluoroquinolones remain effective against penicillin- and macrolide-resistant strains, and are rarely associated with multidrug resistance. However, although fluoroquinolone resistance re-

Table I. Susceptibility* of *Streptococcus pneumoniae* to commonly used antimicrobial agents stratified by susceptibility to penicillin.

Agent	MIC, µg/mL		
	<0.1	0.1–1.0	≥2.0
Amoxicillin	+++	+++	+
Doxycycline	+++	+	+/-
Macrolide†	+++	+	+/-
Cefuroxime	+++	+	–
Fluoroquinolone‡	+++	+++	+++

Reproduced with permission.²

MIC = minimum inhibitory concentration.

*Susceptibility: +++ = ≥90%; ++ = ≥75%; + = ≥50%; +/- = ≥40%; – = <40%.

†Erythromycin, azithromycin, or clarithromycin.

‡Levofloxacin, gatifloxacin, or moxifloxacin.

mains low, isolated cases of resistant *S pneumoniae* infections have been reported in the United States, emphasizing the need for judicious use of these agents.¹⁵

CLINICAL EFFICACY

Clinical trials have consistently shown that fluoroquinolone monotherapy is at least as effective as monotherapy or combination therapy with other antimicrobials.^{16–19} A meta-analysis²⁰ of 8 controlled trials comparing an oral fluoroquinolone with oral macrolide or beta-lactam treatments for CAP concluded that fluoroquinolone-treated patients received modestly better therapeutic benefit compared with non-fluoroquinolone-treated patients. Due to its longer history on the US market, levofloxacin remains the most studied of the respiratory fluoroquinolones for CAP. Several trials have shown that levofloxacin achieved >90% clinical success for mild to severe CAP, including penicillin- and macrolide-resistant *S pneumoniae* infections.^{21–24} In individual clinical trials,^{16,19,25,26} 7 to 14 days of once-daily treatment with levofloxacin 500 mg IV or PO, gatifloxacin 400 mg IV or PO, or moxifloxacin 400 mg PO achieved similar clinical success rates. In a comparative, randomized, double-blind trial that directly compared gatifloxacin and levofloxacin for the treatment of CAP,²⁷ no significant differences were observed in the clinically assessable patients (96% of 163 patients achieved clinical response with gatifloxacin; 93% of 176 patients with levofloxacin).

SAFETY

The safety of respiratory fluoroquinolones has been the focus of many reports,^{25,28–30} and they have been found to be generally well tolerated (**Table II**^{25,29,31–33}). A meta-analysis²⁰ of 8 clinical trials reported that fluoroquinolone therapy was discontinued in 1.8% to 8.4% of patients with CAP due to intolerance; this was comparable to discontinuation rates observed with other antimicrobial agents (eg, oral macrolides and beta-lactams). Gastrointestinal disturbances are the most common adverse effects with fluoroquinolone use, and gatifloxacin and moxifloxacin tend to have higher rates than levofloxacin.^{29,34,35} Central nervous system events (eg, dizziness, headache) are also common, although rates are typically ≤5%.^{28,29,35} The incidence of tendinopathy with the respiratory fluoroquinolones is low, although the risk increases for certain patients, including men, the elderly, patients with renal dysfunction, and patients using corticosteroids.³⁶

Drug interactions are uncommon with the respiratory fluoroquinolones,^{25,29} but their bioavailability might decrease with coadministration of metal-ion-containing drugs, including antacids and mineral supplements.^{25,29} Renal dysfunction decreases the clearance rate of gatifloxacin and levofloxacin, thereby requiring dose adjustment in these patients.^{31,32} However, in general,

Table II. Adverse events observed in clinical trials with the respiratory fluoroquinolones.

Adverse Event	Agent/Reference								
	Levofloxacin			Gatifloxacin			Moxifloxacin		
	25	29	PI* ³¹	25	29	PI* ³²	25	29	PI* ³³
Gastrointestinal									
Nausea		+	+	+++	++	+++	+++	+++	+++
Vomiting	±	±	±		+	±/++		+	±/++
Diarrhea		+	+		++	++	+++	+++	+++
Central nervous system									
Dizziness	±	±	±		+	++		++	++
Headache		±	±			++			±/++
Allergic									
Rash	±	±	±	±		±/++	±		±/++
Pruritus	—		±	—		±/++	±		±/++
Phototoxicity	±	±		—	—		—	—	
Taste perversion	±	±	±		++	±/++			±/++

PI = product information; — = not observed; ± = observed in <1% of patients; + = observed in 1% to <3% of patients; ++ = observed in 3% to 5% of patients; +++ = observed in >5% of patients.

*Data from product information; adverse events were reported as possibly drug related.

clinically significant changes have not been observed in the pharmacokinetic properties of fluoroquinolones based on the age of adults.³⁷ For elderly patients with reduced renal function, creatinine clearance should be monitored to limit the risk for overexposure of fluoroquinolones.³⁸

Well-publicized withdrawals of selected fluoroquinolones from the US market have raised the question of serious toxicities with the class as a whole, but it appears that most of these events are product specific.^{28,30} For example, clinafloxacin, lomefloxacin, and sparfloxacin have been associated with significant phototoxicity,^{28,29,35} temafloxacin has been associated with anaphylaxis and hemolytic anemia,^{30,39} and sparfloxacin and grepafloxacin have been associated with prolongation of the QT interval, increasing the risk for torsades de pointes.³⁰ Consequently, these agents are no longer marketed in the United States. Trovafloxacin has been linked to cases of severe hepatotoxicity, restricting its use to patients for whom the potential benefits outweigh the risks of therapy.^{25,29}

The currently available respiratory fluoroquinolones do not appear to be associated with the majority of these product-specific severe adverse events, but rare cases of severe episodes have been reported, particularly with cardiovascular effects.^{40,41} The prescribing information for levofloxacin,³¹ gatifloxacin,³² and moxifloxacin³³ includes warnings about the potential for cardiotoxicity, and moxifloxacin has been shown to increase the QT interval in a dose-dependent fashion.⁴² QT interval prolongation has been reported with levofloxacin therapy. However, a single dose of levofloxacin up to 1000 mg has not been shown to significantly increase the QT interval compared with placebo.⁴³

Gatifloxacin has been associated with severe episodes of hyper- and hypoglycemia in diabetic and nondiabetic patients, and therefore should be used with some caution.^{44,45}

In general, antimicrobial use has been associated with unintended effects on the commensal flora of patients, often termed “collateral damage.” Reports have linked the use of some cephalosporins with an increase in the incidence of *Clostridium difficile*-associated diarrhea and the presence of vancomycin-resistant enterococci in hospitalized patients.^{46,47} Theoretically, agents such as clindamycin with high activity against anaerobes, particularly *Bacteroides* spp, and agents that pass through the gastrointestinal system in significant amounts, such as ciprofloxacin, will affect the gut flora to a greater extent. Among the respiratory fluoroquinolones, gatifloxacin and moxifloxacin have higher activity against *Bacteroides* spp compared with levofloxacin.²⁵ In addition, ~25% of a moxifloxacin dose passes through the intestinal system as active drug. Levofloxacin and gatifloxacin are primarily excreted renally, and <5% of active drug passes through the gut.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

The respiratory fluoroquinolones are well absorbed after oral dosing, allowing equivalent IV and PO dosing. Each fluoroquinolone has also been shown to preferentially distribute into alveolar macrophages and pulmonary epithelial lining fluid, the sites of infection in CAP.²⁵ Finally, their long half-lives, combined with their pharmacodynamic properties, permit once-daily dosing of fluoroquinolones.

The fluoroquinolones were the first antimicrobial class for which extensive pharmacodynamic assessments were performed during clinical development. Therefore, an understanding of the basic concepts of fluoroquinolone pharmacodynamic properties can greatly assist clinical dose selection in the management of CAP.

Some of the antimicrobials that are commonly used for CAP (eg, the beta-lactams) have time-dependent (or concentration-independent) bactericidal activity. For these agents, the optimal clinical outcome results from maintaining the serum drug concentration above the MIC for the pathogen for the longest possible duration. This is achieved by using small, frequent doses of these agents. The fluoroquinolones exhibit concentration-dependent activity, and the best predictors of clinical efficacy are the ratio of peak concentration to MIC ($C_{\max}/\text{MIC}$) and the ratio of the area under the concentration-time curve to MIC (AUC/MIC). Because neither measure has been conclusively demonstrated to be a better indicator of outcomes, the pharmacodynamic goal of fluoroquinolone therapy is to maximize both $C_{\max}/\text{MIC}$ and AUC/MIC . *S pneumoniae* is effectively eradicated and the emergence of resistance is prevented at an AUC/MIC ratio of ≥ 30 .⁴⁸ For gram-negative infections, an AUC/MIC ratio of ≥ 125 , or a $C_{\max}/\text{MIC}$ ratio of 10, is typically required for effective eradication.

Surveillance data⁴⁹ suggest that gatifloxacin and moxifloxacin are more active than levofloxacin because their MIC₉₀ values against *S pneumoniae* are 0.25 to 0.50 µg/mL, compared with 1.0 µg/mL for levofloxacin. However, levofloxacin achieves higher AUC and C_{max} values than do gatifloxacin and moxifloxacin at the recommended doses for CAP. Thus, all respiratory fluoroquinolones achieve sufficient AUC values to surpass the target AUC/MIC ratio of 30 (**Table III**⁴⁸). The pharmacokinetic and pharmacodynamic properties of levofloxacin may contribute to the equivalent clinical efficacy achieved with this agent compared with the newer fluoroquinolones.

DOSING AND COST OF TREATMENT

Traditional dosing of the fluoroquinolones for CAP is levofloxacin 500 mg, gatifloxacin 400 mg, or moxifloxacin 400 mg, QD for 7 to 14 days. Duration of therapy varies depending on the severity of the illness and specific patient characteristics (eg, age, comorbidities). Pricing of each dose, as determined by the 2003 average wholesale price,⁵¹ is similar for all agents (**Table IV**). Short-course therapies for CAP, such as the 750-mg, 5-day course of levofloxacin, may reduce the overall treatment cost for outpatients.

NOVEL TREATMENT OPTIONS FOR CAP

In the 1950s, the antibiotic regimens for treatment of pneumococcal pneumonia used IM procaine penicillin. Doses were given every 12 hours and continued for ~48 hours after definite clinical improvement, often resulting in a total antibiotic course of 4 to 7 days.⁵² In subsequent decades, controlled clinical trials that used treatment durations of 10 to 14 days for CAP became common. This

Table III. Unbound area under the concentration-time curve (AUC) and AUC/minimum inhibitory concentration (MIC) ratios for the respiratory fluoroquinolones.⁴⁸

Subjects/Agent	Unbound AUC, µg/mL·h*	AUC/MIC, µg/mL				
		2.0	1.0	0.5	0.25	0.125
Healthy volunteers						
Levofloxacin 500 mg	34	17	34	67	134	269
Levofloxacin 750 mg ⁵⁰	57	29	57	114	228	456
Gatifloxacin 400 mg	27	14	27	54	109	217
Moxifloxacin 400 mg	24	12	24	48	96	192
Patients with infection						
Levofloxacin 500 mg	51	25	51	102	203	406
Gatifloxacin 400 mg	41	21	41	82	164	328

*Unbound AUC determined for the 750-mg dose based on the estimate that 30% of levofloxacin is bound.

Table IV. Cost of treatment with respiratory fluoroquinolones.

Regimen	Cost	
	US\$/d*	US\$/Regimen†
Levofloxacin 500 mg QD for 10 d	9.73	97.30
Levofloxacin 750 mg QD for 5 d	11.79	58.95
Gatifloxacin 400 mg QD for 10 d	9.40	94.00
Moxifloxacin 400 mg QD for 10 d	9.80	98.00

*Cost per day was based on average wholesale price as reported in the 2003 Drug Topics Red Book.⁵¹

†Cost per regimen was calculated by multiplying cost/d by the duration of the regimen (in days).

longer duration of therapy was also influenced by patients' expectations that they would continue antibiotics while still symptomatic with cough or chest discomfort, even though these were postinfectious symptoms.

The longer durations of therapy studied in clinical trials and prescribed by most physicians were somewhat counterbalanced by the tendency of patients to discontinue (or forget to use) outpatient oral antibiotic therapy once they were feeling better.⁵³ It has also been shown that compliance with recommended dosing regimens was inversely proportional to the total number of doses per day.^{54,55}

The growing concern over antibacterial resistance has led to investigations of new treatment strategies that limit the emergence of resistance. Recommendations from the World Health Organization⁵⁶ favor the use of potent antibacterial agents for the shortest duration necessary for effective treatment. Theoretically, a high-dose, short-course regimen might provide an effective new treatment option for CAP. Because fluoroquinolones are concentration-dependent agents, a higher dose would increase the AUC and $C_{\max}$ values achieved, potentially resulting in more rapid and complete eradication of pathogens. The short course would decrease total antimicrobial use and, thus, reduce any unnecessary drug exposure of the commensal flora. The short course has the added advantage of possibly improving patient adherence to therapy,^{57,58} which may decrease clinical failures and reduce the risk for resistance development due to premature discontinuation of antimicrobial therapy.

The concentration-dependent activity of the fluoroquinolones makes them excellent candidates for investigating the utility of high-dose, short-course regimens. For levofloxacin, the 750-mg dose approximately doubles the $C_{\max}$ and AUC values compared with the 500-mg dose.⁵⁹ In vitro pharmacodynamic analysis⁶⁰ has shown that the 750-mg dose more rapidly eradicates *S pneumoniae*, and effectively kills less susceptible organisms, including ciprofloxacin-resistant strains of *S pneumoniae*. A clinical trial⁶¹ compared the efficacy and safety of a 750-mg, 5-day levofloxacin regimen with a 500-mg, 10-day levofloxacin course. Each regimen achieved comparable clinical efficacy and microbiologic eradication (>90%), regardless of the causative pathogen. When patients

were stratified according to disease severity, the 750-mg, 5-day course was found to be effective for severe CAP (Pneumonia Severity Index⁶² classes III and IV). The higher levofloxacin dose was also shown to be well tolerated and consistent with the established safety profile of the agent. Interestingly, a greater proportion of patients receiving levofloxacin 750 mg were reported to have fever resolved by day 3 of therapy ($P = 0.006$). More rapid resolution of symptoms may have important clinical consequences, such as earlier hospital discharge and/or faster return to work. The benefits of a high-dose, short-course treatment need to be further studied to fully understand the clinical and economic implications.

The primary limitation of dose escalation with antimicrobials is the potential for adverse events. During the development of ciprofloxacin, the use of 600 mg IV q12h was proposed on the basis of efficacy, but 400 mg IV q8h was chosen for high-dose therapy on the basis of safety.⁶³ The safety profile of levofloxacin 750 mg QD is comparable to the safety profiles of 250 or 500 mg QD,⁵⁰ so safety does not appear to limit high-dose, short-course therapy with this agent. In addition to its US Food and Drug Administration–approved use for CAP, the 750-mg levofloxacin dose is also approved for the treatment of complicated skin and skin-structure infections and nosocomial pneumonia. However, as mentioned earlier, adverse events may restrict the use of higher doses of the other respiratory fluoroquinolones, particularly with regard to the dose-dependent QT interval prolongation associated with moxifloxacin use.⁴³

As with empiric therapy with any antimicrobial, the optimal dosing regimen for a respiratory fluoroquinolone provides adequate bactericidal activity, clinical efficacy, and acceptable tolerability/safety, without promoting the development of resistance. Currently approved dosages of the respiratory fluoroquinolones (levofloxacin 500 mg and 750 mg, gatifloxacin 400 mg, or moxifloxacin 400 mg, QD for 7–14 days) appear to satisfy these criteria. The higher dosage of levofloxacin (750 mg QD) is well tolerated and may provide the additional benefits of increased peak and AUC values that allow a decrease in the duration of therapy, which may increase patient compliance and allow more rapid symptom resolution.

CONCLUSIONS

The respiratory fluoroquinolones are well tolerated and effective for the outpatient management of CAP. Levofloxacin, gatifloxacin, and moxifloxacin have been shown to have broad-spectrum activity against the most common pathogens associated with CAP, and the convenience of once-daily dosing and safety with these agents make them appropriate for first-line treatment in selected patients. The high tissue drug concentrations and excellent tolerability achievable with the 750-mg levofloxacin dose have made it a candidate for short-course (5-day) therapy for CAP. Because isolated cases of fluoroquinolone-resistant *S pneumoniae* have been reported, these potent antimicrobial agents

must be used at an appropriate dose and in the appropriate patients to maximize their value in the treatment of CAP.

ACKNOWLEDGMENT

This article was sponsored by Ortho-McNeil Pharmaceutical, Inc. (Raritan, New Jersey).

REFERENCES

1. Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med*. 1995;333:1618–1624.
2. Bartlett JG, Dowell SF, Mandell LA, et al, for the Infectious Diseases Society of America. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2000;31:347–382.
3. Mandell LA, Bartlett JG, Dowell SF, et al, for the Infectious Diseases Society of America. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis*. 2003;37:1405–1433.
4. Niederman MS, Mandell LA, Anzueto A, et al, for the American Thoracic Society. 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. 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.
6. Marston BJ, Plouffe JF, File TM Jr, et al, for the Community-Based Pneumonia Incidence Study Group. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. *Arch Intern Med*. 1997;157:1709–1718.
7. 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.
8. Bochud P-Y, Moser F, Erard P, et al. Community-acquired pneumonia. A prospective outpatient study. *Medicine (Baltimore)*. 2001;80:75–87.
9. Karlowsky JA, Thornsberry C, Jones ME, et al, for the TRUST Surveillance Program. Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: Results from the TRUST Surveillance Program (1998–2002). *Clin Infect Dis*. 2003;36:963–970.
10. Doern GV, Heilmann KP, Huynh HK, et al. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. *Antimicrob Agents Chemother*. 2001;45:1721–1729.
11. Jones ME, Karlowsky JA, Blosser-Middleton R, et al. Longitudinal assessment of antipneumococcal susceptibility in the United States. *Antimicrob Agents Chemother*. 2002;46:2651–2655.
12. Jacobs MR, Felmingham D, Appelbaum PC, Gruneberg RN, for the Alexander Project Group. The Alexander Project 1998–2000: Susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J Antimicrob Chemother*. 2003;52:229–246.

13. Lynch JP 3rd, Martinez FJ. Clinical relevance of macrolide-resistant *Streptococcus pneumoniae* for community-acquired pneumonia. *Clin Infect Dis*. 2002;34(Suppl 1): S27–S46.
14. Lonks JR. What is the clinical impact of macrolide resistance? *Curr Infect Dis Rep*. 2004;6:7–12.
15. Resistance of *Streptococcus pneumoniae* to fluoroquinolones—United States, 1995–1999. *MMWR Morb Mortal Wkly Rep*. 2001;50:800–804.
16. File TM Jr, 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.
17. Fogarty C, Siami G, Kohler R, et al. Multicenter, open-label, randomized study to compare the safety and efficacy of levofloxacin vs ceftriaxone sodium and erythromycin followed by clarithromycin and amoxicillin/clavulanate in the treatment of serious community-acquired pneumonia in adults. *Clin Infect Dis*. 2004;38(Suppl 1): S16–S23.
18. Fogarty C, Dowell M, Ellison W, et al. Treating community-acquired pneumonia in hospitalized patients: Gatifloxacin vs ceftriaxone/clarithromycin. *J Respir Dis*. 1999;20(Suppl 11):S60–S69.
19. Fogarty C, Grossman C, Williams J, et al. Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. *Infect Med*. 1999;16:748–763.
20. Salkind AR, Cuddy PG, Foxworth JW. Fluoroquinolone treatment of community-acquired pneumonia: A meta-analysis. *Ann Pharmacother*. 2002;36:1938–1943.
21. Fogarty CM, Greenberg RN, Dunbar L, et al. Effectiveness of levofloxacin for adult community-acquired pneumonia caused by macrolide-resistant *Streptococcus pneumoniae*: Integrated results from four open-label, multicenter, phase III clinical trials. *Clin Ther*. 2001;23:425–439.
22. Fogarty CM, Sullivan JG, Chattman MS, et al. Once a day levofloxacin in the treatment of mild to moderate and severe community-acquired pneumonia in adults. *Infect Dis Clin Pract*. 1998;7:400–407.
23. Akpunonu B, Michaelis J, Tennenberg A, et al. Multicenter, postmarketing assessment of levofloxacin in the treatment of adults with community-acquired pneumonia. *Clin Infect Dis*. 2004;38(Suppl 1):S5–S15.
24. Kahn JB, Wiesinger BA, Xiang J. Macrolide-resistant *Streptococcus pneumoniae* in community-acquired pneumonia: Clinical and microbiological outcomes for patients treated with levofloxacin. *Clin Infect Dis*. 2004;38(Suppl 1):S24–S33.
25. Zhanel GG, Ennis K, Vercaigne L, et al. A critical review of the fluoroquinolones: Focus on respiratory infections [published correction appears in *Drugs*. 2002;62: 944]. *Drugs*. 2002;62:13–59.
26. File TM Jr, Schlemmer B, Garau J, et al, for the 049 Clinical Study Group. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: A randomized, double-blind comparison with trovafloxacin. *J Antimicrob Chemother*. 2001; 48:67–74.
27. Sullivan JG, McElroy AD, Honsinger RW, et al. A double-blind, randomized study of safety and efficacy: Treating community-acquired pneumonia with once-daily gatifloxacin vs once-daily levofloxacin. *J Respir Dis*. 1999;20(Suppl 10):S49–S59.
28. Bertino J Jr, Fish D. The safety profile of the fluoroquinolones. *Clin Ther*. 2000;22: 798–817.

29. Fish DN. Fluoroquinolone adverse effects and drug interactions. *Pharmacotherapy*. 2001;21(Suppl):S253–S272.
30. Mandell L, Tillotson G. Safety of fluoroquinolones: An update. *Can J Infect Dis*. 2002; 13:54–61.
31. Levaquin[®] (levofloxacin) [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceuticals, Inc; 2003.
32. Tequin[™] (gatifloxacin) [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2002.
33. Avelox[®] (moxifloxacin hydrochloride) [package insert]. West Haven, Conn: Bayer Corporation; 2002.
34. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: A review focusing on newer agents. *Clin Infect Dis*. 1999;28:352–364.
35. Ball P, Mandell L, Niki Y, Tillotson G. Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Saf*. 1999;21:407–421.
36. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: A critical review of the literature. *Clin Infect Dis*. 2003;36:1404–1410.
37. Chien SC, Chow AT, Natarajan J, et al. Absence of age and gender effects on the pharmacokinetics of a single 500-milligram oral dose of levofloxacin in healthy subjects. *Antimicrob Agents Chemother*. 1997;41:1562–1565.
38. Stahlmann R, Lode H. Fluoroquinolones in the elderly: Safety considerations. *Drugs Aging*. 2003;20:289–302.
39. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: Review of 95 cases. *Clin Infect Dis*. 1994;18:946–950.
40. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy*. 2001;21:1468–1472.
41. Owens RC Jr, Ambrose PG. Torsades de pointes associated with fluoroquinolones. *Pharmacotherapy*. 2002;22:663–668; discussion 668–672.
42. Demolis JL, Kubitz D, Tenneze L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther*. 2000;68:658–666.
43. Noel GJ, Natarajan J, Chien S, et al. Effect of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther*. 2003;73:292–303.
44. Baker SE, Hangii MC. Possible gatifloxacin-induced hypoglycemia. *Ann Pharmacother*. 2002;36:1722–1726.
45. Menzies DJ, Dorsainvil PA, Cunha BA, Johnson DH. Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. *Am J Med*. 2002;113:232–234.
46. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile*-associated diarrhoea: A systematic review. *J Antimicrob Chemother*. 2003;51: 1339–1350.
47. Donskey CJ, Chowdhry TK, Hecker MT, et al. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N Engl J Med*. 2000;343:1925–1932.
48. Gunderson BW, Ross GH, Ibrahim KH, Rotschafer JC. What do we really know about antibiotic pharmacodynamics? *Pharmacotherapy*. 2001;21(Suppl 11):S302–S318.
49. 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.

50. Chien SC, Wong FA, Fowler CL, et al. Double-blind evaluation of the safety and pharmacokinetics of multiple oral once-daily 750-milligram and 1-gram doses of levofloxacin in healthy volunteers. *Antimicrob Agents Chemother.* 1998;42:885–888.
51. *2003 Drug Topics® Red Book®.* Montvale, NJ: Thomson PDR; 2003.
52. Witt RL, Hamburger M. The nature and treatment of pneumococcal pneumonia. *Med Clin North Am.* 1963;47:1257–1270.
53. Awunor-Renner C. Length of antibiotic therapy in in-patients with primary pneumonias. *Ann Trop Med Parasitol.* 1979;73:235–240.
54. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296–1310.
55. Kardas P. Once-daily dosage secures better compliance with antibiotic therapy of respiratory tract infections than twice-daily dosage. *J Appl Res.* 2003;3:201–206.
56. World Health Organization (WHO) Web site. Overcoming antimicrobial resistance: World Health Organization Report on Infectious Diseases 2000. WHO/CDS/2000.2. 2000. Geneva, Switzerland: WHO; 2000. Available at: www.who.int/infectious-disease-report/2000/intro.htm. Accessed May 15, 2004.
57. Reyes H, Guiscafne H, Munoz O, et al. Antibiotic noncompliance and waste in upper respiratory infections and acute diarrhea. *J Clin Epidemiol.* 1997;50:1297–1304.
58. Schrag SJ, Pena C, Fernandez J, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: A randomized trial. *JAMA.* 2001;286:49–56.
59. Gotfried MH, Danziger LH, Rodvold KA. Steady-state plasma and intrapulmonary concentrations of levofloxacin and ciprofloxacin in healthy adult subjects. *Chest.* 2001;119:1114–1122.
60. Lister PD. Pharmacodynamics of 750 mg and 500 mg doses of levofloxacin against ciprofloxacin-resistant strains of *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis.* 2002;44:43–49.
61. Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: A new treatment paradigm [published correction appears in *Clin Infect Dis.* 2003;37:1147]. *Clin Infect Dis.* 2003;37:752–760.
62. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997;336:243–250.
63. Echols RM. The approval process for intravenous ciprofloxacin. *Infect Med.* 1992;9(Suppl D):23–31.

Address correspondence to: Hans H. Liu, MD, FACP, Bryn Mawr Medical Specialists Association, 933 Haverford Road, Bryn Mawr, PA 19010. E-mail: liuliang@aol.com