

Guide to Selection of Fluoroquinolones in Patients with Lower Respiratory Tract Infections

Wael E. Shams^{1,2,3} and Martin E. Evans¹

- 1 Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine, Lexington, Kentucky, USA
- 2 Department of Internal Medicine, University of Alexandria Faculty of Medicine, Alexandria, Egypt
- 3 Division of Infectious Diseases, Department of Internal Medicine, East Tennessee State University, Johnson City, Tennessee, USA*

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* Current affiliation.

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Abstract

Newer fluoroquinolones such as levofloxacin, moxifloxacin, gatifloxacin and gemifloxacin have several attributes that make them excellent choices for the therapy of lower respiratory tract infections. In particular, they have excellent intrinsic activity against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and the atypical respiratory pathogens. Fluoroquinolones may be used as monotherapy to treat high-risk patients with acute exacerbation of chronic bronchitis, and for patients with community-acquired pneumonia requiring hospitalisation, but not admission to intensive care. Overall, the newer fluoroquinolones often achieve clinical cure rates in $\geq 90\%$ of these patients. However, rates may be lower in hospital-acquired pneumonia, and this infection should be treated on the basis of anticipated organisms and evaluation of risk factors for specific pathogens such as *Pseudomonas aeruginosa*. In this setting, an antipseudomonal fluoroquinolone may be used in combination with an antipseudomonal β -lactam.

Concerns are now being raised about the widespread use, and possibly misuse, of fluoroquinolones and the emergence of resistance among *S. pneumoniae*, Enterobacteriaceae and *P. aeruginosa*. A number of pharmacokinetic parameters such as the peak concentration of the antibacterial after a dose (C_{\max}), and the 24-hour area under the concentration-time curve (AUC_{24}) and their relationship to pharmacodynamic parameters such as the minimum inhibitory and the mutant prevention concentrations (MIC and MPC, respectively) have been proposed to predict the effect of fluoroquinolones on bacterial killing and the emergence of resistance. Higher C_{\max}/MIC or AUC_{24}/MIC and C_{\max}/MPC or AUC_{24}/MPC ratios, either as a result of dose administration or the susceptibility of the organism, may lead to a better clinical outcome and decrease the emergence of resistance, respectively. Pharmacokinetic profiles that are optimised to target low-level resistant minor subpopulations of bacteria that often exist in infections may help preserve fluoroquinolones as a class. To this end, optimising the AUC_{24}/MPC or C_{\max}/MPC ratios is important, particularly against *S. pneumoniae*, in the setting of lower respiratory tract infections. Agents such as moxifloxacin and gemifloxacin with high ratios against this organism are preferred, and agents such as ciprofloxacin with low ratios should be avoided. For agents such as levofloxacin and gatifloxacin, with intermediate ratios against *S. pneumoniae*, it may be worthwhile considering alternative dose administration strategies, such as using higher dosages, to eradicate low-level resistant variants. This must, of course, be

balanced against the potential of toxicity. Innovative approaches to the use of fluoroquinolones are worth testing in further *in vitro* experiments as well as in clinical trials.

Lower respiratory tract infections include acute bronchitis, acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).

Acute bronchitis is an inflammatory condition of the tracheobronchial tree in which cough, with or without sputum production, is a predominant feature in the absence of physical and radiographic findings of pneumonia.^[1] It is one of the most commonly encountered disease entities in clinical practice.^[2] Acute bronchitis may be due to underlying infectious or noninfectious triggers.^[3] Microbiological studies of acute bronchitis identify aetiological pathogens in only 40% of cases at most. Of these, bacteria are only responsible for 5–20% of episodes, while viruses are thought to be the underlying aetiology in the remainder.^[3] Important viruses include the influenza viruses, parainfluenza viruses, respiratory syncytial virus and common cold viruses such as the corona viruses and the rhinoviruses.^[1,3,4] Bacterial causes of acute bronchitis are less common. Important aetiologies include *Bordetella pertussis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. *Streptococcus pneumoniae* and *Haemophilus influenzae* do not seem to be causative agents in acute bronchitis, although they may play a role in secondary infection since they are a part of the resident respiratory flora.^[1,3,5] The diagnosis of acute bronchitis depends mainly on the physical examination and radiography to exclude signs of pneumonia.^[1] Routine sputum Gram-stain and culture are of low yield in detecting *B. pertussis*, *M. pneumoniae* or *C. pneumoniae*.^[3]

Chronic bronchitis is defined as the presence of a productive cough for 3 months in each of 2 successive years in a patient in whom other causes of cough, such as infection with *Mycobacterium tuberculosis*, carcinoma of the lung, bronchiectasis, cystic fibrosis or chronic congestive heart failure, have been excluded.^[6] Chronic bronchitis and emphyse-

ma often occur together because both are frequent results of aetiological factors such as exposure to cigarette smoke. These two disease entities represent the spectrum of chronic obstructive pulmonary disease (COPD), which afflicts 30 million individuals in the US alone.^[6] AECB in these patients is characterised by increased cough and sputum production and worsening dyspnoea resulting in respiratory decompensation without an objectively documented cause such as pneumonia.^[1,6-8] The role of bacterial infection as an underlying aetiology for AECB has been debated.^[9,10] Increases in the production of purulent sputum, the presence of neutrophils and bacteria in the sputum and the appearance of an acute antibody response to respiratory pathogens suggest that bacteria play a central role in this process.^[11-17] Also of note, several placebo-controlled trials have documented a better outcome for patients with AECB treated with antibacterials.^[18-20] One remarkable study performed in Tunisia compared the use of ofloxacin to placebo for patients with exacerbations of COPD requiring mechanical ventilation. The combined frequency of death in hospital and the need for additional antibacterials was significantly lower in the patients given ofloxacin (absolute risk reduction 45.9%; 95% CI 29.1, 62.7; $p < 0001$), and the duration of mechanical ventilation and hospital stay was shorter in the treated group (absolute difference 4.2 days, 95% CI 2.5, 5.9 and 9.6 days, 95% CI 3.4, 12.8, respectively).^[21]

A recent review of several longitudinal studies of groups of patients with COPD concluded that 80% of AECB episodes were infectious in origin, with 40–60% caused by bacteria such as *H. influenzae*, *Moraxella catarrhalis*, *S. pneumoniae*, *H. parainfluenzae* and *Pseudomonas aeruginosa*.^[12,14,22] Patients with significant structural lung impairment, as manifested by a forced expiratory volume in 1 second (FEV₁) <50%, were more likely to be infected with *H. influenzae* or *P. aeruginosa*.^[14] Approxi-

mately 30% of infections were caused by viruses such as the influenza and respiratory syncytial viruses, and 5–10% were caused by atypical bacteria such as *Legionella* spp., *M. pneumoniae* or *C. pneumoniae*.^[12]

Pneumonia ranks first as the cause of death from infection and sixth as the leading cause of death in general in the US. More than 2 million cases of CAP occur each year in the US, resulting in approximately 10 million physician visits, more than 500 000 hospitalisations and 50 000 deaths.^[23–25] The Infectious Diseases Society of America (IDSA) practice guidelines define CAP as “an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds or localised rales), in a patient not hospitalised or residing in a long-term-care facility for ≥ 14 days before onset of symptoms”.^[26] Symptoms of acute lower respiratory infection often include two or more of the following: fever or hypothermia, rigors, sweats, new cough with or without sputum production or change in colour of respiratory secretions in a patient with chronic cough, chest discomfort or the onset of dyspnoea. Many patients also have nonspecific symptoms, such as fatigue, myalgias, abdominal pain, anorexia and headache.^[26]

CAP may be viral, bacterial or fungal in aetiology; however, a causative pathogen may not be identified in up to 50–60% of patients despite extensive laboratory testing.^[26–29] Aetiological viruses include the influenza viruses, respiratory syncytial virus, adenovirus, parainfluenza virus, herpes simplex virus, Hantavirus and the SARS coronavirus.^[30–35] The most commonly encountered bacteria include *S. pneumoniae* (20–60%), *H. influenzae* (2–31%), *M. catarrhalis* (2–13%) and ‘atypical bacteria’ such as *M. pneumoniae* (13–37%), *C. pneumoniae* (6–17%) and the *Legionella* species (1–16%).^[24–26,36–40] Coinfection with atypical bacterial pathogens is estimated to occur in up to 48% of all patients with CAP.^[41,42] Enteric Gram-negative bacteria are not common causes of CAP, yet they may be encoun-

tered in particular settings (see section 7.3).^[28,43,44] *Pneumocystis jirovecii* (formerly *carinii*) and endemic fungi (*Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*) constitute other aetiological agents that are often dependent on epidemiological and host factors.^[26,45,46] The frequency of these pathogens varies with the setting in which the infection was acquired. Variables include the season of the year, geographical location, environmental exposure and host factors such as age, smoking, alcohol use and underlying illnesses.^[26,39,44]

HAP is defined as an inflammatory condition of the lung parenchyma occurring ≥ 48 hours after hospital admission and caused by infectious agent(s) not present or incubating at the time of admission. HAP is the second most common nosocomial infection and the leading cause of hospital morbidity and mortality.^[47,48] HAPs are mainly bacterial in aetiology. Gram-negative pathogens, Gram-positive pathogens and polymicrobial infections are responsible for 55–85%, 20–30% and 40–60% of the cases, respectively. Causative Gram-negative bacteria include *P. aeruginosa*, *Enterobacter* spp. and *Acinetobacter* spp., while causative Gram-positive bacteria include *Staphylococcus aureus* and *S. pneumoniae*.^[47,49] HAP developing on the third or fourth day of hospitalisation, i.e. early-onset HAP, is usually caused by the same pathogens as CAP.

A number of antimicrobial agents have been used for the treatment of lower respiratory tract infections, but perhaps the newest and most efficacious antibacterials are the fluoroquinolones. Leshner et al.^[50] introduced the prototype quinolone, nalidixic acid, in 1962. Nalidixic acid became a commonly used antibacterial for the treatment of uncomplicated urinary tract infections because it reliably covered the Enterobacteriaceae. However, nalidixic acid use in systemic infections was limited because of its low serum and tissue concentrations, narrow antibacterial spectrum and the emergence of bacterial resistance.^[51,52] Numerous quinolone derivatives of nalidixic acid were developed and studied over the subsequent two decades until fluoroquinolones with improved pharmacokinetic and pharmacody-

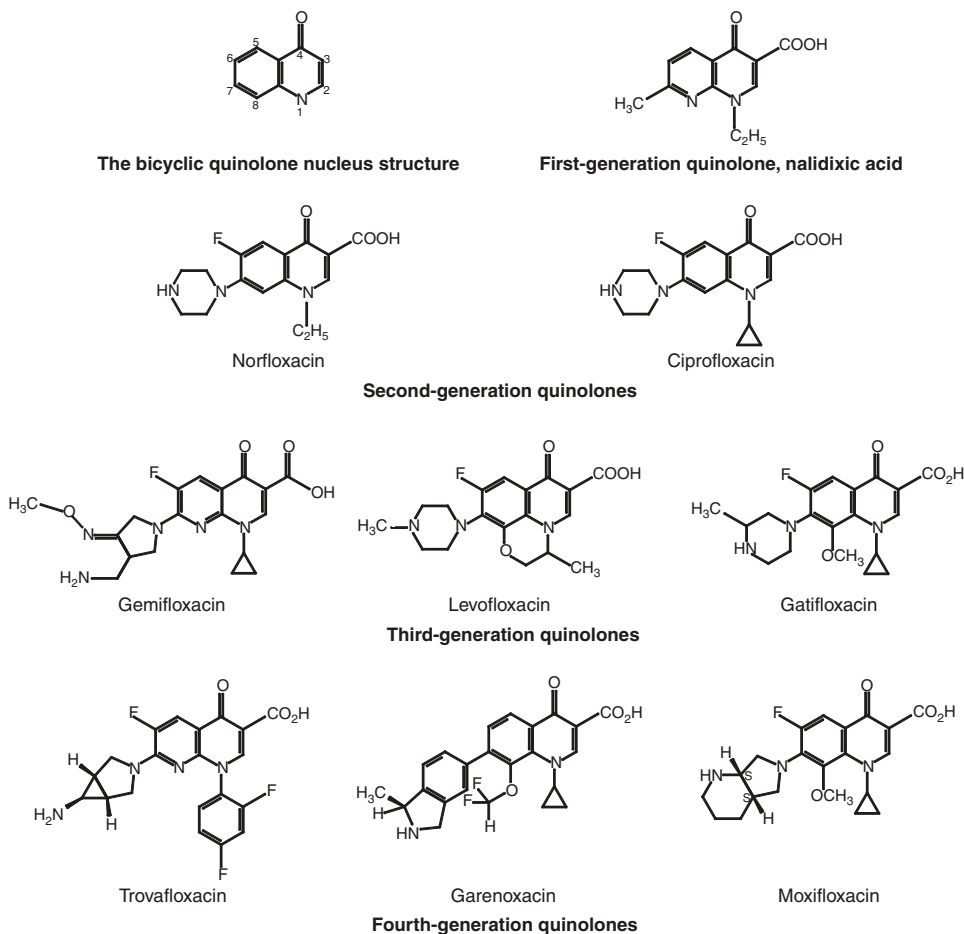


Fig. 1. Bicyclic quinolone nucleus and structural representatives of the four generations of quinolones.

namic properties were introduced and approved for clinical use. Placement of a fluorine atom at the 6 position of the quinolone nucleus (figure 1) and replacement of the 7-methyl side-chain of nalidixic acid with a piperazine group markedly enhanced microbiological activity.^[53,54] These fluoroquinolones, such as ciprofloxacin, had an extended Gram-negative spectrum, but still lacked reliable coverage of important Gram-positive respiratory pathogens such as *S. pneumoniae*. This limited their role to clinical settings such as AECB, nosocomial pneumonia and cystic fibrosis, where Gram-negative bacilli were the predominant pathogens. Recently, fluoroquinolones such as levofloxacin, moxifloxacin and gatifloxacin have been introduced.

These agents possess excellent activity against *S. pneumoniae* and atypical respiratory pathogens such as *Legionella pneumophila*, *M. pneumoniae* and *C. pneumoniae*.^[55] However, concerns are now being raised about their widespread use, and possibly misuse, because of increasing reports of fluoroquinolone resistance among *S. pneumoniae*, Enterobacteriaceae and *P. aeruginosa*.^[56-58]

Recently, several excellent reviews of the use of fluoroquinolones in respiratory tract infections have appeared.^[59-62] The following is an update of data in this rapidly evolving field with an emphasis on the use of fluoroquinolones in clinical practice.

1. Classification of Quinolones According to Structure and Microbiological Spectrum

The following classification system is based on the integration of both microbiological susceptibilities and pharmacokinetic data.^[63] Early agents had moderate activity against Gram-negative bacteria but their pharmacokinetics relegated them to the treatment of urinary tract infections and sexually-transmitted diseases. Chemical modifications to the quinolone nucleus led to agents with enhanced activity against Gram-negatives and improved pharmacokinetics. This was followed by alterations which led to improved activity against *S. pneumoniae* and anaerobes, while retaining the improved pharmacokinetic properties.

1.1 First-Generation Quinolones

The key features of first-generation quinolones are:

- poor serum and tissue concentrations, therefore inadequate for the treatment of systemic infections;
- useful for urinary tract infections and sexually transmitted diseases; and
- lack significant activity against *P. aeruginosa*, Gram-positive bacteria and anaerobes.

This group includes the original quinolones, nalidixic acid and cinoxin, which share either a bicyclic quinolone nucleus, or the naphthyridone derivative of this nucleus with a nitrogen atom at the 8 position (figure 1). These agents are available for oral use only. Their use has been limited to uncomplicated urinary tract infections because they do not achieve adequate serum and tissue concentrations, and they lack significant activity against *P. aeruginosa*, Gram-positive bacteria and anaerobes.^[64,65]

1.2 Second-Generation Quinolones

The key features of second-generation quinolones are:

- late members achieve adequate serum and tissue concentrations and can be used to treat systemic infections;

- excellent Gram-negative activity including *P. aeruginosa*; and
- only modest activity against methicillin-resistant *S. aureus* (MRSA), weak activity against *S. pneumoniae* and no significant anaerobic activity.

This group includes norfloxacin, lomefloxacin, enoxacin, ofloxacin and ciprofloxacin. The addition of a fluorine atom at the 6 position of the quinolone nucleus and replacement of the 7-methyl side-chain of nalidixic acid with a piperazine group (figure 1) markedly enhance microbiological activity of these agents and allow coverage of a wide range of Gram-negative bacteria, including *P. aeruginosa*.^[53,54] Early members of this group, such as norfloxacin, lomefloxacin and enoxacin, are only available orally, and have been relegated to the treatment of urinary tract infections because they do not achieve adequate serum or tissue concentrations. Replacement of the 1-ethyl group of norfloxacin with a cyclopropyl moiety and further structural changes at the 1, 7 and 8 positions of the quinolone nucleus have led to the synthesis of ofloxacin and ciprofloxacin (figure 1). These later compounds have improved pharmacokinetic properties enabling them to achieve excellent serum and tissue concentrations with either oral or intravenous use. This has allowed their widespread use in urinary tract as well as systemic infections. They are also concentrated in pulmonary alveolar macrophages. This gives them enhanced activity against intracellular pathogens such as *Chlamydia*, *Mycoplasma* and *Legionella* spp. Despite these advances, the second-generation agents lack adequate activity against important Gram-positive bacteria, such as MRSA and *S. pneumoniae*, and have no clinically useful activity against anaerobic bacteria.^[64,65]

1.3 Third-Generation Quinolones

The key features of third-generation quinolones are:

- improved pharmacokinetics allowing once daily dose administration; and
- enhanced activity against *S. pneumoniae*.

This group includes levofloxacin, sparfloxacin, grepafloxacin, gatifloxacin and gemifloxacin. Levofloxacin is the *l*-isomer of ofloxacin. Other agents in this group have further structural changes such as a modification of the piperazine group at C7 of the quinolone nucleus with addition of methyl groups, alkylation of the ring structure at the 7 position, and the addition of a methoxy group at the 8 position (figure 1). These structural changes improve the pharmacokinetics of these compounds, allowing single daily dose administration, and enhance their activity against *S. pneumoniae*.^[53,64,65] These drugs also have enhanced antimicrobial activity against *Legionella*, *Chlamydia* and *Mycoplasma* spp.^[66,67] On the basis of minimum inhibitory concentrations (MICs), third-generation quinolones such as levofloxacin may be less active than second-generation quinolones such as ciprofloxacin against *P. aeruginosa*.^[65] However, reports of clinical failures with levofloxacin in *P. aeruginosa* infections are rare. This may be because the *in vitro* disadvantage of levofloxacin may be compensated for by a pharmacokinetic profile in patients which results in superior blood and tissue concentrations.^[68-70] Grepafloxacin has been removed from the market because of its significant potential for life-threatening tachyarrhythmias caused by corrected QT (QTc) interval prolongation, and sparfloxacin has been removed from the market because of unacceptable phototoxicity. Gemifloxacin is the most recent member in this group with enhanced activity against *S. pneumoniae*, and variable activity against anaerobes. It has recently gained US FDA approval for use in CAP and AECB.

1.4 Fourth-Generation Quinolones

The key feature of fourth-generation quinolones is enhanced activity against anaerobes.

This group includes trovafloxacin, clinafloxacin, moxifloxacin and garenoxacin. Further structural modification, such as a halogen substitution at the 8 position of the quinolone (clinafloxacin) or the use of a naphthyridone nucleus in place of the quinolone nucleus, results in enhanced antimicrobial activity against anaerobes such as *Bacteroides fragilis*, in

addition to coverage of aerobic Gram-positive and Gram-negative organisms. Although moxifloxacin is active *in vitro* against anaerobes, its efficacy in treating anaerobic infections has not been established and its use for such infections is not approved by the US FDA.^[64,71] The US FDA has advised reserving trovafloxacin therapy for life-threatening infections requiring inpatient treatment because of the risk of hepatotoxicity.^[72] Clinafloxacin has been withdrawn from the market because of its significant phototoxicity.

Garenoxin is a novel des-fluoro(6) quinolone with a broad antimicrobial spectrum of coverage similar to trovafloxacin. The removal of fluorine atom at C6 differentiates this drug from other fluoroquinolones and may decrease toxicity.^[73-75] It has not yet been released on the market. Despite initial reports of a favourable safety profile,^[76] hypotension was encountered more with garenoxacin than with its comparator drugs in phase III clinical trials. The clinical significance of this adverse effect has not yet been determined. After a re-evaluation of its antibacterial research and development priorities, the developing company (Bristol-Myers Squibb) recently announced that the product will be reacquired by the initial licensing company (Toyama Chemical).^[77]

2. Mechanism of Action and Resistance

Quinolones kill bacteria when they bind and inhibit the activity of bacterial topoisomerases, particularly topoisomerase II (DNA gyrase) and topoisomerase IV. These enzymes are essential for bacterial DNA synthesis and maintenance. DNA gyrase, encoded by the *gyrA* and *gyrB* genes, induces negative supercoils in DNA, whereas topoisomerase IV, encoded by the *parC* and *parE* genes (designated *grlA* and *grlB* in *S. aureus*), is involved in DNA decatenation.^[61,78] DNA gyrase is the primary target for most quinolones against Gram-negative bacteria, and topoisomerase IV is the primary target for most Gram-positive bacteria, although exceptions occur.^[79-84]

Resistance to quinolones arises when spontaneous mutations occur in the *parC/E* (*grlA/B*) or *gyrA/*

B genes.^[85,86] It is not due to acquisition of resistance genes as is the case in macrolide (*ermAM* or *mefE* genes) or methicillin (*SCCmec*) resistance. Thus, fluoroquinolone resistance can arise *de novo* from many different geographic foci rather than from the spread of a single clone. The appearance of ciprofloxacin resistance in Canada, for instance, is thought to be due to the selective pressure of fluoroquinolone use upon multiple indigenous, unrelated strains throughout the country.^[87] The horizontal spread of a resistant clone may still occur, although this appears to be uncommon to date.^[88]

In Gram-positive organisms, single-step mutations in the *parC/E* (*grlA/B*) genes cause low-level resistance to ciprofloxacin, and mutations in the *gyrA/B* genes alone are usually not associated with a change in phenotype. High-level resistance occurs only when there are mutations in both *parC/E* (*grlA/B*) and *gyrA/B* genes.^[89] *GyrA* may be the primary target with other fluoroquinolones and bacteria. Data from *in vitro* assays show that single-step mutations occur in *S. aureus* and *S. pneumoniae* with frequencies often ranging from 10^{-6} to 10^{-8} .^[90-95] Thus, single-step, low-level resistant variants are probably common in many pulmonary infections since the bacterial numbers can often exceed 10^8 colony forming units (cfu)/g of tissue.^[96] If these variants are not eradicated, a second mutation may lead to high-level resistance.

Resistance may also be the result of decreased outer membrane permeability or efflux pumps.^[55] The latter is an energy-dependent process that limits the intracellular accumulation of antibacterials. It results in low-level resistance, and may or may not occur in conjunction with mutations in topoisomerase genes.^[55,61,97,98] Efflux affects the activity of norfloxacin and ciprofloxacin more than levofloxacin, gatifloxacin and gemifloxacin. The activity of moxifloxacin and trovafloxacin are affected the least.^[99-102]

Important differences may exist in the ability of specific fluoroquinolones to select resistant variants among Gram-positive respiratory pathogens. For instance, ciprofloxacin selects resistant variants of *S. pneumoniae in vitro* more readily than grepaflox-

acin, gemifloxacin, trovafloxacin, levofloxacin, moxifloxacin, gatifloxacin or garenoxacin.^[91,94,95,103-106] It also selects resistant variants of methicillin-sensitive or -resistant *S. aureus* more frequently than levofloxacin, trovafloxacin, gatifloxacin or garenoxacin.^[90,92,93,107-109] Overall, the 8-methoxy quinolones, gatifloxacin and moxifloxacin, and the des-fluoro(6) quinolone, garenoxacin, appear to select resistant mutants of *S. pneumoniae* and *S. aureus* at a lower rate than the older quinolones.^[103,104,110,111] It is not clear why these differences exist, but it may be a function of the intrinsic activity of the compounds themselves against the bacteria. For instance, one study showed that the most active compound against *S. pneumoniae* was gemifloxacin (MIC = 0.03 µg/mL), followed by clinafloxacin (MIC = 0.06 µg/mL), trovafloxacin (MIC = 0.12 µg/mL), grepafloxacin and moxifloxacin (MIC = 0.25 µg/mL), gatifloxacin (MIC = 0.5 µg/mL), levofloxacin (MIC = 1 µg/mL) and ciprofloxacin (MIC = 2 µg/mL).^[112] These intrinsic activities of the compounds combined with their pharmacokinetic profiles may be the key to understanding their ability to thwart (or foster) the emergence of resistance (see discussion on pharmacodynamics in section 3).

The insights into resistance seen in *in vitro* assays have been predictive of the performance of fluoroquinolones in clinical practice. For instance, failures of ciprofloxacin to cure pneumococcal infections have been well documented (table I). Several patients developed meningitis while on therapy, and in some clinical trials employing ciprofloxacin for the treatment of AECB, *S. pneumoniae* was found to persist in the sputum in up to 50% of treated patients and 57% of treatment failures were due to the organism.^[113] The US FDA subsequently modified the package insert to suggest that ciprofloxacin not be used as a drug of first choice for the treatment of presumed or confirmed pneumonia due to *S. pneumoniae*.^[114] Failures with levofloxacin have also been reported (table II). As with ciprofloxacin, several of the patients developed meningitis while on therapy, leading one group to suggest that a β-lactam drug be used along with levofloxacin until

Table I. Clinical failures with ciprofloxacin

Study	Location, date reported	Patient age/sex (M/F)	Diagnosis	Underlying illness	Ciprofloxacin dosage	Outcome
Davies et al. ^[118]	The Netherlands, 1986	80 patients divided into four groups	AECB	COPD	500mg po bid or 750mg po bid or 1000mg po bid	17 of 26 patients who had <i>Streptococcus pneumoniae</i> infections failed therapy
Cooper and Lawlor ^[119]	Connecticut, USA, 1989	57 M	CAP	None	500mg po bid then tid	Cured when switched to penicillin
Frieden and Mangi ^[120]	Connecticut, USA, 1990	34 M	Otitis, mastoiditis, bacteraemia	Splenectomy	750mg bid	ND
Righter ^[121]	Toronto, Canada, 1991	77 F	CAP, bacteraemia	Polymyalgia rheumatica receiving corticosteroids	200mg IV bid	Developed meningitis
Gordon and Kauffman ^[122]	Michigan, USA, 1990	61 M	HAP	Cholecystitis; Hx of resected lung cancer	200mg IV bid	ND
Perez-Trallero et al. ^[123]	Spain, 1990	84 M	CAP	None	200mg IV bid then 500mg po bid	Cured when switched to amoxicillin
Lee et al. ^[124]	USA, 1991	32 M	<i>Shigella</i> enteritis	ND	500mg bid	Developed <i>S. pneumoniae</i> sinusitis and pneumonia, recovered
		65 M	Otitis	ND	250mg bid	Developed meningitis, died
		43 F	URTI	ND	500mg bid	Developed meningitis, recovered
		31 F	URTI	ND	750mg bid	Developed meningitis, pneumonia, bacteraemia
Kimbrough et al. ^[125]	Missouri, USA, 1988	65 M	Otitis	Chronic renal failure	250mg bid	Developed pneumococcal meningitis and bacteraemia and died despite switching to penicillin therapy
		43 F	URTI	Hx of Hodgkin's disease, status post-splenectomy and radiation therapy	500mg bid	Developed pneumococcal meningitis. Cured when switched to IV penicillin and ceftriaxone
Colville et al. ^[126]	UK, 1994	75 F	CAP	COPD	500mg po bid	Cured when switched to amoxicillin
	UK, 1994	72 M	AECB	COPD	250mg po bid	Cured when switched to amoxicillin + erythromycin
Mouton et al. ^[127]	France, 1990	8 patients	CAP	ND	750mg po bid	ND
Weiss et al. ^[117]	Montreal, Canada, 1995–6	77 M	AECB	COPD	ND	Cured when switched to ceftriaxone
		80 M	AECB	COPD	ND	Cured when switched to ceftriaxone
		77 M	AECB	COPD	ND	Cured when switched to erythromycin
		59 M	HAP	COPD	ND	Death despite switching to cefuroxime
		87 M	AECB	COPD	ND	Cured when switched to erythromycin
		77 M	AECB	COPD	ND	Cured when switched to ceftriaxone

AECB = acute exacerbation of chronic bronchitis; **bid** = twice daily; **CAP** = community-acquired pneumonia; **COPD** = chronic obstructive pulmonary disease; **F** = female; **HAP** = hospital-acquired pneumonia; **Hx** = history; **IV** = intravenous; **M** = male; **ND** = no data; **po** = oral; **tid** = three times daily; **URTI** = upper respiratory tract infection.

Table II. Clinical failures with levofloxacin

Study	Location, date reported	Patient age/sex (M/F)	Diagnosis	Underlying illness	Drug dosage	Outcome
Wortman and Bennett ^[128]	Washington, DC, USA, 1999	58 M	Sinusitis, fever	HIV, splenectomy	Levofloxacin 500mg po od	Death, meningitis
Kuehnert et al. ^[129]	Georgia, USA, 1999	63 M	CAP	ND	Levofloxacin, not given	Survived when switched to ceftriaxone
Ross et al. ^[115]	Massachusetts, USA, 1999	79 M	CAP	ND	Levofloxacin, not given	Death, meningitis
Empey et al. ^[130]	Kentucky, USA, 2001	53 M	CAP	None	Levofloxacin 500mg IV od	Survived, switched to ceftriaxone
Urban et al. ^[131]	New York, USA, 2001	50 M	AECB	COPD	Levofloxacin 500mg IV od	Survived, switched to co-trimoxazole
Davidson et al. ^[132]	Nova Scotia, Canada, 2000	84 M	AECB	COPD	Levofloxacin 500mg IV od	Survived, switched to clindamycin/ceftazidime
		64 M	CAP	ND	Levofloxacin 500mg po od	ND
		37 F	CAP	None	Levofloxacin 500mg po od	ND
	Ontario, Canada, 2002	66 F	CAP	Chronic lymphocytic leukaemia, COPD	Ciprofloxacin 500mg po bid for 8 days, then levofloxacin 500mg po od	Death
	British Columbia, Canada, 2001	80 F	AECB	COPD	Ciprofloxacin 500mg po bid for 6 days, then levofloxacin 500mg po od	ND
Kays et al. ^[133]	Indiana, USA, 2002	50 M	CAP	COPD, diabetes mellitus	Levofloxacin 500mg IV od	Survived, treated with ceftriaxone
Davies and Maesen ^[134]	The Netherlands, 1999	20 patients	AECB	ND	Levofloxacin 250mg po od	6/11 failures
					Levofloxacin 500mg po od	7/9 failures

AECB = acute exacerbation of chronic bronchitis; **bid** = twice daily; **CAP** = community-acquired pneumonia; **COPD** = chronic obstructive pulmonary disease; **F** = female; **IV** = intravenous; **M** = male; **ND** = no data, **od** = once daily, **po** = oral.

the results of susceptibility testing become available.^[115] Of note, many patients in this study who failed levofloxacin therapy had been previously exposed to fluoroquinolones. This has also been reported by others.^[116,117] Failures to other fluoroquinolones have not been reported to date, but may occur with increased use of the drugs.

One area of particular concern is cross-resistance among fluoroquinolones. The use of one agent can lead to class resistance to all fluoroquinolones. Johnson noted that 88% (29/33) of isolates with ciprofloxacin MICs >8 µg/mL in one study were also resistant to moxifloxacin,^[135] and Weiss reported an outbreak of fluoroquinolone-resistant *S. pneumoniae* in a hospital ward where ciprofloxacin was often used as empirical therapy for lower respiratory tract infections. This outbreak involved 16 patients with organisms that had either single (*parC*) or double (*parC* and *gyrA*) mutations leading to low-level (4 µg/mL) or high-level (16 µg/mL) resistance to ciprofloxacin, respectively. Cross-resistance with levofloxacin (MIC 8 µg/mL), moxifloxacin and gatifloxacin (MIC 2 µg/mL) was observed.^[117] In another study, Urban and coworkers reported two patients who failed levofloxacin therapy. The isolates from these patients had increased MICs to gatifloxacin, moxifloxacin and trovafloxacin. No data was available about prior exposure to ciprofloxacin.^[131] These reports mirror the cross-resistance among fluoroquinolones seen after *in vitro* exposure of *S. pneumoniae* to ciprofloxacin,^[95,109,112] and raise concerns that misuse of older fluoroquinolones may select low-level resistant variants that then become highly resistant to all fluoroquinolones with a second mutation.^[131,132]

Although resistance to fluoroquinolones has been reported *in vitro* and in isolated patients, the prevalence of resistance among *S. pneumoniae* and other respiratory pathogens in large geographic areas over time has remained low (table III). Sahm and coworkers^[136,137] were some of the first to examine fluoroquinolone resistance rates among respiratory pathogens. They reported that only 0.3% of 5640 *S. pneumoniae* isolates collected from 1997 and 1998 after 10 years of ciprofloxacin use in the US were

resistant to ciprofloxacin.^[136] However, when this group compared isolates collected during the 1997–8 respiratory season with those collected in 1998–9, they found a statistically significant increase in levofloxacin resistance from 0.1% to 0.6%.^[137] (table III). Others have also examined resistance to the newer fluoroquinolones among *S. pneumoniae*. For instance, Brueggemann et al. examined a large group of isolates from the US collected in 1994–5 and 1999–2000, and found that resistance rates to levofloxacin, gatifloxacin and moxifloxacin were low and had remained stable.^[138] Doern et al. found that only 0.3% of a large number of isolates were resistant to levofloxacin and that there was no change over 5 years of observation.^[139] Thornsberry and Sahm found the same results when comparing isolates collected during the respiratory seasons of 1998–9 and 1999–2000.^[140] The same group found that resistance to levofloxacin among children was low, perhaps reflecting the relative lack of use of fluoroquinolones in this population.^[141] The US Centers for Disease Control and Prevention (CDC) reported isolates recovered from invasive pneumococcal disease and found that ofloxacin resistance had increased from 2.6% in 1995 to 3.8% in 1997, but there was no increase in levofloxacin resistance during that interval.^[142] Sahm et al.^[143] reported a slightly higher rate of levofloxacin resistance in isolates collected in the 2001–2 respiratory season. An analysis of isolates collected from community-based practices in the US instead of hospital-based laboratories showed no resistance to either levofloxacin or gatifloxacin.^[40] Karchmer^[144] reported the results of the PROTEKT US (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States) study where 10 103 isolates were collected during the 2000–1 respiratory season from 206 sites in 41 states. Overall, levofloxacin resistance rates were low and varied geographically from 0% (in the Southeast) to 1.3% (in the Northeast). However, resistance rates were higher in some areas of the country. Rates were highest in Massachusetts (4.8%), Colorado (4.6%) and Alaska (2%), and in cities such as Salem, Massachusetts (21.8%), Stam-

Table III. Reported resistance rates of *Streptococcus pneumoniae* to fluoroquinolones^a

Study	Year(s) isolates collected	Location	Number of isolates tested	Percentage intermediate or resistant		
				levofloxacin	gatifloxacin	moxifloxacin
Sahm et al. ^[137]	1997–8, 1998–9	USA	7246	0.1–0.6	ND	ND
Brueggemann et al. ^[138]	1994–5, 1999–2000	USA	4650	0.3–0.5	0.2–0.3	0.1–0.3
Doern et al. ^[139]	1994–5, 1997–8 to 1999–2000	USA	1531	0.3	0.3	0.3
Thornsberry and Sahm ^[140]	1998–2000	USA	13 795	0.5–0.6	ND	ND
Karlowsky et al. ^[141]	2000–2	USA	2834	0.7–1.3	ND	ND
CDC ^[142]	1995–9	USA	15 292	0.2	ND	ND
Pfaller and Jones ^[40]	2000	USA	682	0	0	ND
Sahm et al. ^[143]	2001–2	USA	4922	0.8	ND	ND
Karchmer ^[144]	2000–1	USA	10 103	0–1.3	ND	ND
Chen et al. ^[56]	1988–98	Canada	7551	0.37	0.36	0.29
Zhanel et al. ^[112]	1997–2002	Canada	6991	0.6	0.6	0.3
Powis et al. ^[147]	2002	Canada	2539	2.2	2.0	1.4
Buxbaum et al. ^[148]	1994–6	Austria	1385	<1	0	0
Johnson et al. ^[135]	1998–9	England and Wales	807 (surveillance) 462 (referred)	ND ND	ND ND	0.9 5.8
Glatz et al. ^[149]	2000	Hungary	96	4.2	ND	ND
Oteo et al. ^[150]	1999–2000	Spain	300	0.4	ND	ND
Decousser et al. ^[151]	2000	France	112	ND	1	ND
Dobay et al. ^[152]	1999–2002	Hungary	304	0	0	0
Hsueh and Luh ^[153]	1998–9	Taiwan	267	1	ND	ND
Sahm et al. ^[154]	1997–8	Europe, Asia	1879	0.3	ND	ND
Song et al. ^[155]	2000–1	Asia	685	1.6	1.6	0.3
Hoban et al. ^[156]	1997–9	Worldwide	8252	0.1–0.7	0.1–1	ND
Jones et al. ^[157]	1997–2000	Worldwide	10 978	0.4	0.3	ND
Felmingham et al. ^[158]	1999–2000	Worldwide	3362	1 (14.3 in Hong Kong)	ND	1 (14.3 in Hong Kong)
Ho et al. ^[159]	1998	Hong Kong	181	4.4	ND	ND
Ho et al. ^[160]	2000	Hong Kong	30	13.3	12.2	8.9

a Isolates were intermediate or resistant with breakpoints as follows: levofloxacin ≥ 4 mg/mL, moxifloxacin and gatifloxacin ≥ 2 mg/mL.^[146]

CDC = Centers for Disease Control and Prevention; ND = no data.

ford, Connecticut (11.8%), Dayton, Ohio (5.9%) and Denver, Colorado (5.6%).^[145]

Fluoroquinolone resistance trends have also been examined in other countries. In a longitudinal study in Canada, Chen et al.^[56] reported that the prevalence of ciprofloxacin-resistant *S. pneumoniae* strains increased from 0% in 1988 to 1.7% in 1997 and 1998. This was seen most commonly in adults and not children, reflecting the use of fluoroquinolones in Canada. The resistance to the newer fluoroquinolones remained low. Zhanel and co-

workers^[112] examined almost 7000 *S. pneumoniae* isolates collected throughout Canada from 1997 through 2002 and found that $\leq 1.1\%$ were resistant to levofloxacin. However, they noted that cross-resistance among the fluoroquinolones was common. Isolates that were resistant to levofloxacin had increased MICs to ciprofloxacin, gatifloxacin, moxifloxacin, gemifloxacin and garenoxacin. Powis and coworkers^[147] examined 2539 isolates collected as part of the Canadian Bacterial Surveillance Network in 2002 and reported levofloxacin resistance rates of

2.17%. This was an increase from 1.0% reported 2 years before.

An analysis of 1385 *S. pneumoniae* strains collected in Austria from 1994 to 1996 showed that levofloxacin resistance was rare, and there was no resistance to moxifloxacin or gatifloxacin.^[148] In the UK, Johnson et al.^[135] found a high prevalence of moxifloxacin resistance among isolates referred for additional testing because of resistance to 'first-line agents', but the prevalence of resistance was much lower among isolates collected in routine surveillance activities. Glatz and coworkers^[149] from Hungary also found higher rates of fluoroquinolone (levofloxacin) resistance among isolates that were resistant to other agents (in this case penicillin). A low level of resistance to the newer fluoroquinolones was reported from several other small collections of isolates from other European countries, and a relatively low level of levofloxacin resistance was reported in a small series from Taiwan.^[150-153] Song et al.^[155] reported resistance rates of *S. pneumoniae* isolates collected from 11 Asian countries during the 2000-1 respiratory season and reported that resistance was higher with levofloxacin and gatifloxacin than with moxifloxacin.

Several large studies have attempted to monitor the prevalence of fluoroquinolone resistance among *S. pneumoniae* worldwide. For instance, Sahm and coworkers^[154] reported on a large number of isolates collected from China, Japan and several European countries during the winter of 1997-8. They found a low prevalence of resistance to levofloxacin among *S. pneumoniae*. Hoban et al.^[161] reported data from the SENTRY Antimicrobial Surveillance Program, and found a low worldwide prevalence of resistance to levofloxacin and gatifloxacin. However, when the data from North America were examined for trends in resistance, it was found that the rate of resistance to levofloxacin among *S. pneumoniae* had increased from 0.3% in 1997-8 to 0.9% in 1999.^[162] In another study, resistance was more common in the Asia-Pacific region (0.8-0.9%), followed by North America (0.4-0.5%) and Europe and Latin America (0.1-0.2%).^[157] The worldwide prevalence of resistance to levofloxacin and moxifloxacin in the PRO-

TEKT surveillance study was around 1%. The exception was Hong Kong, where more than 14% of the isolates were resistant to the two antibacterials.^[158] Similar high resistance rates in Hong Kong were also reported by Ho and colleagues.^[159,160]

In summary, resistant *S. pneumoniae* can readily be selected *in vitro* and failures among patients treated with ciprofloxacin and levofloxacin have been well documented. However, to date resistance rates to the newer fluoroquinolones among *S. pneumoniae* appear to be low, although several studies suggest that rates are increasing in localised areas of the world. Studies have shown that fluoroquinolone resistance is more common among persons ≥ 65 years of age in contrast to penicillin resistance, which is more common in children. This may reflect the relative use of the antibacterials in these age groups.^[142] This may change if fluoroquinolones are approved for paediatric use. Cross-resistance among fluoroquinolones has been seen and is of concern.^[112] Thus, overuse of older agents may result in loss of efficacy of the newer agents. Also of note, fluoroquinolone resistant isolates are often resistant to other classes of antibacterial as well.^[135,138,149] Among the organisms resistant to levofloxacin reported by the CDC, 60% were also resistant to penicillin, 53% were resistant to cefotaxime, 33% were resistant to erythromycin and 60% were resistant to co-trimoxazole (trimethoprim/sulfamethoxazole).^[142] Similar trends have been reported by others.^[163] *H. influenzae* has been reported to be resistant to ciprofloxacin.^[164] To date, *H. influenzae* and *M. catarrhalis* have remained sensitive to the newer fluoroquinolones.^[140,154,156,165,166]

3. Pharmacokinetics and Pharmacodynamic Considerations

The efficacy of an antibacterial against pathogens is often expressed in terms of the MIC. The MIC is defined as the concentration of antibacterial that results in no net growth of an inoculum of 5×10^5 bacteria after incubation for 18 hours. Laboratory techniques for determining the MIC as well as the interpretive breakpoints used for labelling an organism as sensitive, intermediate or resistant to the

antibacterial have been published and are currently used by most clinical laboratories.^[167] Although the MIC has been used successfully for the management of patients in the past, this statistic is proving to be of limited value for predicting the emergence of resistance to fluoroquinolones.

Recently, investigators have focused on the effect of antibacterials on the selection of resistant variants, and proposed that environments providing small differences in antibacterial concentrations could have a selective effect on bacterial cultures comprised of subpopulations of heterogenous resistance phenotypes. These 'selective windows' or compartments are bounded by the concentration that inhibits susceptible bacteria (MIC) and the concentration that inhibits organisms with low-level resistance.^[168] Negri and coworkers^[169,170] examined the effect of antibacterial exposures on mixtures of penicillin-susceptible and -resistant *S. pneumoniae* and TEM-1 and TEM-12 β -lactamase-producing *Escherichia coli* having different MICs, and showed that resistant strains were most readily selected at antibacterial concentrations within the selective

compartment. Dong and colleagues^[171] suggested that similar principles govern the selection of resistant variants of *S. aureus* exposed to fluoroquinolones. They defined a 'mutant selective window' as the antimicrobial concentration range that falls between the MIC and the mutant prevention concentration or MPC (the concentration that inhibits growth of first-step mutants) [figure 2]. They reported experimental data and theoretical analyses suggesting that regimens providing fluoroquinolone concentrations that fall within the selective window select resistant *S. aureus* strains, whereas regimens providing concentrations above the MPC prevent the emergence of resistant strains.^[171-174] This work has been expanded into a theoretical analysis of the effect of fluoroquinolones on *S. pneumoniae*,^[172] but to date, the exact relationship between pharmacokinetic profiles and the bacterial MIC and MPC (delimiting the selective window) have not been defined.

A number of pharmacokinetic parameters and their relationship to pharmacodynamic parameters

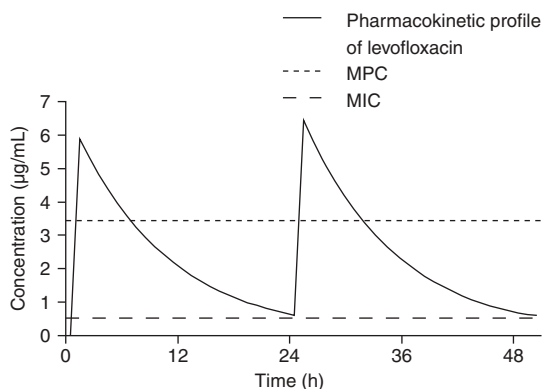


Fig. 2. Pharmacokinetic profile of levofloxacin administered at a dose of 500mg intravenously every 24 hours. The minimum inhibitory concentration (MIC) and mutant prevention concentration (MPC) delimit the 'mutant selective window'.

(MIC or MPC) have been proposed to predict the effect of fluoroquinolones on bacterial killing and the emergence of resistance. The most common pharmacokinetic values examined are the peak concentration of the antibacterial after a dose (C_{max}) and the 24-hour area under the concentration-time curve (AUC_{24}). Experimental evidence has shown that, in many cases, the quinolones kill most rapidly when their concentrations are appreciably above the MIC of the target microorganism. This is known as concentration-dependent or dose-dependent killing (in contrast to time-dependent or concentration-independent killing often seen with β -lactams and macrolides).^[63] Efforts have been made to quantify the relationship between pharmacokinetic parameters (C_{max} , AUC_{24}) and the pharmacodynamic parameter, MIC, to optimise dose administration strategies. To date, there have been no clinical trials examining ratios using the MPC as the divisor.

The value of pharmacodynamic ratios (AUC_{24}/MIC and C_{max}/MIC) for predicting the outcome of fluoroquinolone therapy has been examined in a few studies. Forrest and coworkers analysed the results of ciprofloxacin therapy in seriously ill patients with a variety of infections and concluded that an AUC_{24}/MIC ratio of >125 was an important predictor of clinical and microbiological cure. The applicability of this conclusion to lower-respiratory tract infections is uncertain, however, because infections of

wounds and the urinary tract were included in the analysis, and there were no patients infected with *S. pneumoniae*. The majority of patients were infected with *S. aureus*, *P. aeruginosa* or other Gram-negative aerobes. The conclusions of the study regarding the efficacy of ciprofloxacin may also have been confounded by the concomitant use of rifampin and azlocillin in some patients.^[175] These investigators later examined the effect of three different oral grepafloxacin doses in patients with AECB. The patients were infected with a wide variety of Gram-negative and Gram-positive bacteria of varying susceptibilities to the antibacterial. The authors analysed the aggregate data and concluded that AUC₂₄/MIC values of <75 were inadequate, but values of >175 were sufficient for bacteriological and clinical cure. However, the AUC₂₄/MIC values associated with bacteriological and clinical cure varied with the organism examined. For instance, grepafloxacin-sensitive organisms such as *M. catarrhalis* and *Haemophilus* spp. were eradicated regardless of the AUC₂₄/MIC value, and 88%, 100% and 75% of the *S. pneumoniae* isolates were eradicated at AUC₂₄/MIC values of 0 to 92, >92 to 230 and >230, respectively. In contrast, only 31% of more resistant organisms such as *P. aeruginosa* were eradicated at the lowest AUC₂₄/MIC range, and only 50% were eradicated at the highest range.^[176] Another study performed in patients receiving ciprofloxacin or a β -lactam for nosocomial lower-respiratory tract infections concluded that cure was more likely if the AUC₂₄/MIC was >100. However, the applicability of this conclusion for patients with *S. pneumoniae* or *M. catarrhalis* infections remains uncertain because no patient in the study was infected with these organisms.^[177] Another study that analysed the data from a trial of levofloxacin (sometimes with other drugs) administered for the treatment of nosocomial pneumonia due to a range of Gram-positive and -negative bacteria concluded that an AUC/MIC ratio ≥ 87 was optimal for eradication of the pathogens involved.^[178] Only one trial has examined the ability of the C_{max}/MIC ratio to predict the outcome of fluoroquinolone therapy. On the basis of the results of a large, multicentre trial involving patients with a variety of

pathogens causing respiratory, skin and urinary tract infections treated with levofloxacin, Preston and coworkers concluded that both clinical and microbiological outcomes were more likely to be favourable if the C_{max}/MIC ratio was >12.2.^[179]

Others have examined pharmacodynamic ratios specifically for fluoroquinolones and *S. pneumoniae*. Lacy et al.^[180] studied the effects of ciprofloxacin and levofloxacin against four isolates in an *in vitro* infection model and found that bacterial growth was suppressed by levofloxacin with AUC₂₄/MIC ratios in the range of 30–55. Regrowth occurred with ciprofloxacin up to the highest AUC₂₄/MIC ratio tested of 28.4. In another *in vitro* model, Lister and Sanders^[181] showed that levofloxacin eradicated eight strains if the AUC₂₄/MIC ratios were in the range of 32–64. Ciprofloxacin eradicated five of the strains with AUC₂₄/MIC values of only 44. Craig and Andes^[182] examined the effect of fluoroquinolones on *S. pneumoniae* in a murine thigh infection model and found that there was a 2–2.5 log₁₀ kill of the organisms and 80–90% survival if the AUC₂₄/MIC was >25–35. In a study examining the effect of levofloxacin or gatifloxacin on patients with CAP or AECB caused by *S. pneumoniae* Ambrose et al.^[183] found 100% bacterial eradication if the free-drug AUC₂₄/MIC ratio was >33.7.

Overall, the data from clinical trials are limited and the conclusions from these trials are confusing for the clinician. The studies do suggest that, in general, higher C_{max}/MIC or AUC₂₄/MIC ratios, either as a result of dose administration or the susceptibility of the organism, lead to a better outcome.^[184–186] The exact value of the pharmacodynamic ratio that should be targeted for rapid killing or to prevent resistance remains elusive, probably because of the wide variety of organisms and antibacterials studied, the limited number of isolates tested and the use of different systems (*in vitro*, animal and clinical trials). A more systematic approach using a limited number of organisms under tightly controlled conditions might be more useful for gaining insights into broad pharmacodynamic

principles that could then be applied in tightly controlled clinical trials.^[187]

New insights into the evolution of resistance among bacteria exposed to fluoroquinolones, and in the use of novel dose administration regimens, have been gained through a series of experiments in an *in vitro* pharmacodynamic system. In these experiments, *S. aureus* was exposed to simulated clinical and experimental regimens of ciprofloxacin, and the response of the bacteria was monitored over time. With exposure to clinical regimens (400mg twice or three times daily), the initially sensitive bacteria became resistant, as evidenced by a change of their MIC from 0.5 to 8–16 µg/mL. It was observed that whenever the bacteria were grown to high numbers for the inoculum of the system (2×10^8 cfu), small numbers of bacteria with low-level resistance (MICs in the range of 2–4 µg/mL) would invariably be present. These appeared as a result of spontaneous mutation in the QRDR of *grlA* in many cases. Mathematical modeling of bacterial killing and regrowth in the system as a function of dose administration was done, and the model was used to predict a regimen that would eradicate the culture. This regimen consisted of a single high dose to eradicate the low-level resistant variants present in the inoculum followed by standard dose administration to eradicate the sensitive majority. When the regimen was tested in the *in vitro* system, the culture was eradicated. These experiments suggested that the key to bacterial eradication was to target low-level resistant variants present in the inoculum.^[107,187]

This strategy fits in well with the concept of the MPC, which is the concentration of antibacterial that prevents the appearance of first-step mutants. It has been shown that pharmacokinetic profiles that keep antibacterial concentrations above the MPC prevent the selection of resistant variants and ultimately lead to bacterial eradication in *in vitro* systems.^[107,188] However, the exact relationship of pharmacokinetic profiles to the MPC has yet to be elucidated. Simply keeping the concentration of antibacterial above the MPC may result in unacceptable toxicity. As mentioned earlier, newer fluoroquinolones such as levofloxacin, gatifloxacin,

gemifloxacin, moxifloxacin and garenoxacin are more active than ciprofloxacin against pathogens such as *S. pneumoniae* and *S. aureus*, and appear to have less of a propensity to select resistant variants using clinical dose administration regimens in an *in vitro* system. This may be because the newer fluoroquinolones have better pharmacokinetic profiles than older agents (higher C_{max}/MPC or AUC_{24}/MPC ratios), or because of properties intrinsic to the compounds themselves.^[108,109] The increased activity (lower MIC and MPC) of several of the newer fluoroquinolones, such as moxifloxacin, may allow the clinician to exceed the MPC without producing toxicity.^[172]

Pharmacokinetic parameters of the most commonly encountered fluoroquinolones on the market are presented in table IV. There are potentially important differences among these agents. For instance, the half-life ($t_{1/2}$) of the newer fluoroquinolones ranges from 4.5 to 13.3 hours; their C_{max} varies from 2.97 to 8.6 µg/mL; and the AUC_{24} at steady state (AUC_{24ss}) varies from 9.0 to 91 mg • h/L. Some controversy exists about these values because some investigators believe that only a drug that is not protein bound is biologically active. If protein binding is taken into account, C_{max} values of some compounds, such as gemifloxacin and garenoxacin, must be reduced by 60% and 87%, respectively.^[189] In contrast, other investigators have shown that protein binding has little effect on fluoroquinolone activity.^[190,191] The fact that all the compounds are concentrated in alveolar macrophages (ranging from 11.8-fold of serum C_{max} for ciprofloxacin to 18.2-fold for gatifloxacin) and bronchial epithelial fluids (ranging from 0.63-fold of serum C_{max} for ciprofloxacin to 4.6-fold for moxifloxacin) may be important clinically. However, these data must be interpreted in the context of the MICs and MPCs of pathogens likely to be encountered in lower respiratory tract infections. When ciprofloxacin and the newer fluoroquinolones are compared on the basis of their pharmacokinetic parameters (C_{max} and AUC_{24} with standard dose administration regimens) with the MICs and MPCs of large collections of *S. pneumoniae*, it becomes

Table IV. Pharmacokinetics of ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin in human serum and lung

Drug	Oral dosage (mg)	t _{1/2} (h)	C _{max} ss (µg/mL) ^a	AUC _{24ss} ^a (mg • h/L)	Protein binding (%)	Concentration alveolar macrophages (µg/mL)	Concentration bronchial epithelial lining fluid (µg/mL)
Ciprofloxacin ^[192,193]	500 bid	4.5	2.9	27	20–40	34.9 ^b	1.87 ^b
	750 bid	6.6	3.6	32	ND	ND	ND
Levofloxacin ^[193,194]	500 od	7.6	5.7	48	24–38	98 ^b	10 ^b
	750 od	8.8	8.6	91		105 ^b	22 ^b
Gatifloxacin ^[195,196]	400 od	7.1	4.2	34	20	77 ^{b,c}	6.16 ^{b,c}
Moxifloxacin ^[197,198]	400 od	12.7	4.5	48	50	57 ^{c,d}	20.7 ^{c,d}
Gemifloxacin ^[99,200]	320 od	6.2	1.8	9	55–73	107	2.69
Garenoxacin ^[201]	400 od	13.3	5.0	55	80–85	106 ^{e,f}	9 ^{e,f}

a Steady-state concentrations after multiple dose administration.
 b At 4 hours.
 c Concentrations measured after 400mg single oral dose.
 d At 2.2 hours.
 e At 3 hours.
 f Concentrations measured after 600mg sing oral dose.
AUC_{24ss} = 24-hour area under the concentration-time curve at steady state; **bid** = twice daily; **C_{max} ss** = maximum serum concentration at steady state; **ND** = no data; **od** = once daily; **t_{1/2}** = serum elimination half-life.

evident that ratios differ considerably among fluoroquinolones (table V). For instance, the C_{max}/MIC₉₀ values range from 1.0 to 21.4 and the AUC₂₄/MIC₉₀ values range from 9.5 to 106 (for ciprofloxacin at 500mg and gemifloxacin at 400mg, respectively). Similar differences are apparent when the MPC is used as the divisor and when ratios are calculated for alveolar macrophages and bronchial epithelial lining fluid. At present, interpretation of these values and their application to patient care has yet to be clarified. In general, higher pharmacodynamic ratios in serum, alveolar macrophages and epithelial lining fluid will probably lead to less selection of resistance and better patient outcomes. The exact values that delimit the probabilities of cure or failure remain to be defined.

4. Clinical Trials

4.1 Levofloxacin

4.1.1 Acute Exacerbations of Chronic Bronchitis

Zhanel et al.^[59] reviewed four studies published prior to the first quarter of 2000 where levofloxacin in dosages of 250–500mg each day were compared with cefuroxime axetil or cefaclor for the treatment of AECB. Bacterial eradication rates for levofloxacin ranged from 63% to 68% with clinical success rates ranging from 78% to 95%. The clinical success rates with the cephalosporins were in the range of 48–93%.^[59] Four studies have been published since this review comparing the efficacy of levofloxacin and other agents (table VI). Masterton and Burley^[203] compared 5- and 7-day courses of oral levofloxacin in patients with AECB from 48 centres in ten countries. They found equivalent clinical and microbiological success (more than 80%) for both regimens. Weiss^[204] examined the relative efficacy of levofloxacin, clarithromycin and cefuroxime axetil in patients with AECB. The efficacy and tolerability of the three agents were similar and in all cases was ≥80%. File et al.^[205] reported the results of studies comparing levofloxacin with an enhanced amoxicillin/clavulanic acid formulation (2000mg/125mg) designed for the treatment of penicillin-resistant *S. pneumoniae*. Both regimens were 100%

Table V. Pharmacodynamics of ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin against *Streptococcus pneumoniae*^a

Drug, oral dose	MIC ₉₀ /MPC	Plasma C _{max} ^b /MIC ₉₀	Plasma AUC ₂₄ ^b /MIC ₉₀	Plasma C _{max} ^b /MPC	Plasma AUC ₂₄ ^b /MPC	Alveolar macrophages (C _{max} /MIC ₉₀)	Bronchial epithelial lining fluid (C _{max} /MIC ₉₀)	Alveolar macrophages (C _{max} /MPC)	Bronchial epithelial lining fluid (C _{max} /MPC)
Ciprofloxacin, 500mg	2/ND	1.0	9.5	NA	NA	17.5	0.935	NA	NA
Ciprofloxacin, 750mg		1.3	11.2	NA	NA	NA	NA	NA	NA
Levofloxacin, 500mg	1/8	3.9	32.7	0.5	4.1	98	10	12.3	1.3
Levofloxacin, 750mg		5.9	62.6	0.7	7.8	105	22	13.2	2.8
Gatifloxacin, 400mg	1/4	5.7	27.5	1.4	6.9	154.6 ^c	12.3 ^c	19.3 ^c	1.5 ^c
Moxifloxacin, 400mg	0.5/2	4.6	48	1.15	12	226.8 ^c	82.8 ^c	28.4 ^c	10.4 ^c
Gemifloxacin, 320mg	0.03/1	21.4	106	0.64	3.2	3566	44.8	107	2.69
Garenoxacin, 400mg	0.12/ND	7.4	78.2	NA	NA	884 ^d	76.7 ^d	NA	NA

a MIC₉₀ values from Zhanel et al.^[99] and Hansen et al.^[202] MPC values from Hansen et al.^[202]

b Free drug.

c Ratio calculated using C_{max} obtained after single oral dose of 400mg.

d Ratio calculated using C_{max} obtained after single oral dose of 600mg.

AUC₂₄ = 24-hour area under the concentration-time curve; C_{max} = maximum serum concentration; MIC₉₀ = minimum concentration to inhibit growth of 09% of isolates; MPC = mutant prevention concentration; NA = values not available; ND = no data.

successful in eradicating *S. pneumoniae* from the sputum and curing the patients.^[205] Amsden and coworkers^[206] studied patients recruited from 21 medical centres in the US from August 1999 through May 2000 and showed equivalence of azithromycin and levofloxacin with success rates of more than 80% when the endpoints were clinical cure or improvement of AECB. The numbers were too small to show any difference in the rates of bacterial eradication. Both drugs were equally well tolerated.^[206]

4.1.2 Community-Acquired Pneumonia

Fogarty and colleagues^[207] summarised the results of four studies commissioned by the R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey to study the efficacy of levofloxacin in CAP caused by erythromycin-sensitive and -resistant *S. pneumoniae* (table VI). These studies were independently reported from 1997 through 1999, and the results of one of these studies was commented upon in a previous review of levofloxacin efficacy.^[59] The overall microbiological and clinical success was good (97% and 98%, respectively) and there was no difference among patients infected with erythromycin-sensitive or -resistant organisms. In another study reported by Fogarty et al.,^[210] levofloxacin was compared with ceftriaxone plus erythromycin given intravenously followed by amoxicillin/clavulanic acid plus clarithromycin given orally. The overall clinical success rates and bacteria eradication rates were comparable. Gotfried and coworkers^[208] examined the relative efficacy of oral levofloxacin and an extended-release formulation of clarithromycin for ambulatory patients with CAP during 1999 and 2000. Both agents appeared to be equally efficacious, with microbiological eradication rates ≥80% in most cases and clinical cure or improvement seen in more than 85% of patients.^[208] From 1997 to 1999, Frank and coworkers^[209] compared levofloxacin with a combined regimen of ceftriaxone and azithromycin for patients hospitalised with moderate-to-severe CAP. Both regimens were given for at least 10 days, although ceftriaxone was administered for only the first 2 days to prevent bacteraemia due to *S. pneumoniae*. Both regimens

Table VI. Results of clinical trials of levofloxacin and comparator drugs for lower respiratory tract infections

Study	Design	Regimens	Organism eradication rate	Cure/improvement rate
Acute exacerbation of chronic bronchitis				
Masterton and Burley ^[203]	r, db, mc	Levofloxacin 500mg po od for 5 days	Overall, 81% (52/64) <i>Streptococcus pneumoniae</i> , 75% <i>Haemophilus influenzae</i> , 88% <i>Moraxella catarrhalis</i> , 72%	83% (197/238)
		Levofloxacin 500mg po od for 7 days	Overall, 84% (58/69) <i>S. pneumoniae</i> , 81% <i>H. influenzae</i> , 79% <i>M. catarrhalis</i> , 95%	85% (207/244)
Weiss ^[204]	r, p, mc	Levofloxacin 500mg po od for 10 days	ND	87% (76/87)
		Clarithromycin 500mg po bid for 10 days	ND	88% (80/91)
		Cefuroxime axetil 250mg po bid for 10 days	ND	80% (67/84)
File et al. ^[205]	r, db, dd,	Levofloxacin 500mg po od for 10 days	<i>S. pneumoniae</i> , 100% (7/7)	100% (7/7)
	pl	Amoxicillin/clavulanic acid 2000mg/125mg bid for 10 days	<i>S. pneumoniae</i> , 100% (12/12)	100% (12/12)
Amsden et al. ^[206]	r, db, dd, mc	Levofloxacin 500mg po od for 7 days	Overall, 89% (16/18) <i>S. pneumoniae</i> , 100% <i>H. influenzae</i> , 83% <i>M. catarrhalis</i> , 90%	92% (96/104) day 4, 86% (83/97) day 24
		Azithromycin 500mg po for 1 day, then 250mg for 4 days	Overall, 96% (22/23) <i>S. pneumoniae</i> , 100% <i>H. influenzae</i> , 93% <i>M. catarrhalis</i> , 100%	89% (96/108) day 4, 82% (86/105) day 24
Community-acquired pneumonia				
Fogarty et al. ^[207]	4 × nb, mc	Levofloxacin 500mg po od for 7–14 days	<i>S. pneumoniae</i> , 97% (194/200)	98% (230/235)
Gottfried et al. ^[208]	r, db, mc	Levofloxacin 500mg po od for 7 days	Overall, 88% (136/155) <i>S. pneumoniae</i> , 91% <i>H. influenzae</i> , 96% <i>M. catarrhalis</i> , 86% <i>Chlamydomphila pneumoniae</i> , 80% <i>Mycoplasma pneumoniae</i> , 85%	86% (107/124)
		Clarithromycin extended-release 500mg po od for 7 days	Overall, 87% (134/154) <i>S. pneumoniae</i> , 86% <i>H. influenzae</i> , 78% <i>M. catarrhalis</i> , 82% <i>C. pneumoniae</i> , 93% <i>M. pneumoniae</i> , 90%	88% (113/128)
Frank et al. ^[209]	r	Levofloxacin 500mg IV or po od for ≥10 days	Overall, 92% (33/36)	94% (80/85)
		Azithromycin 500mg IV for ≥2 days plus ceftriaxone 1g IV od for 2 days with switch to azithromycin 500mg po od at the investigator's discretion	Overall, 94% (33/35)	92% (72/78)
Fogarty et al. ^[210]	r, mc	Levofloxacin 500mg IV, then po od for 7–14 days	Overall, 79% (19/24) <i>S. pneumoniae</i> , 80% <i>H. influenzae</i> , 100% <i>C. pneumoniae</i> , 60%	89% (85/95)

Continued next page

Table VI. Contd

Study	Design	Regimens	Organism eradication rate	Cure/improvement rate
		Ceftriaxone 1–2g IV or IM od with erythromycin 500–1000mg IV every 6 hours, then switched to amoxicillin/clavulanic acid, 875mg po bid with clarithromycin 500mg po bid for 7–14 days	Overall, 82% (31/38) <i>S. pneumoniae</i> , 95% <i>H. influenzae</i> , 100% <i>C. pneumoniae</i> , 40%	83% (74/89)
Akpunonu et al. ^[211]	mc, nb	Levofloxacin 500mg od	Overall, 93% (312/334) <i>S. pneumoniae</i> , 93% <i>H. influenzae</i> , 99% <i>M. catarrhalis</i> , 89% <i>Staphylococcus aureus</i> , 91%	94% (1029/1095)
Nosocomial pneumonia				
West et al. ^[212]	r, mc	Levofloxacin 750mg IV od followed by po for 7–15 days	Overall, 67% (62/93)	58% (54/93)
		Imipenem/cilastatin 500mg to 1g every 6–8 hours followed by ciprofloxacin 750mg po every 12 hours for 7–15 days	Overall, 61% (57/94)	61% (57/94)

bid = twice daily; **db** = double-blinded; **dd** = double dummy; **IM** = intramuscular; **IV** = intravenous; **mc** = multicentre; **nb** = nonblind; **ND** = no data; **od** = once daily; **p** = prospective; **pl** = parallel; **po** = oral; **r** = randomised.

were equally efficacious with bacterial eradication and clinical cure or improvement rates exceeding 90%.^[209,210] In a multicentre, postmarketing assessment of levofloxacin efficacy for the treatment of CAP, Akpunonu and coworkers,^[211] reported excellent success against a variety of respiratory pathogens.

4.1.3 Nosocomial Pneumonia

Only one clinical trial has been published which examined the efficacy of one of the new respiratory fluoroquinolones in nosocomial pneumonia. This trial compared a high dose of levofloxacin (750mg given intravenously, then orally) with imipenem/cilastatin followed by oral ciprofloxacin. Other antibacterials could be added if the patient was infected with *P. aeruginosa* or MRSA. The clinical cure and microbiological eradication rates were similar (table VI).^[212]

4.2 Gemifloxacin

4.2.1 Acute Exacerbation of Chronic Bronchitis

Zhanel et al.^[59] reviewed the results of two reports on the use of gemifloxacin for AECB. The first was a randomised, double-blind, multinational study that compared the efficacy and safety of gemifloxacin with trovafloxacin in the treatment of AECB.^[213] Gemifloxacin demonstrated similar effi-

cacy to trovafloxacin with clinical and bacteriological success rates of 91.5% and 87% for gemifloxacin versus 87.6% and 82% for trovafloxacin. These authors also reviewed the preliminary results of the GLOBE (Gemifloxacin Long term Outcomes of Bronchitis Exacerbation) study in which the efficacy and safety of a 5-day course of gemifloxacin were compared with those of a standard 7-day regimen of clarithromycin in patients with AECB (table VII).^[214] Clinical and bacteriological cure rates were comparable in both groups. However, when the impact of treatment on the long-term (26 weeks) clinical outcome was assessed, significantly more patients receiving gemifloxacin than clarithromycin remained free of AECB recurrences (71.0% vs 58.5%, respectively).^[214]

Since the review by Zhanel et al.,^[59] at least four more studies have been published addressing the use of gemifloxacin for AECB and comparing it with other conventional antibacterial regimens (table VII). File and coworkers^[221] compared gemifloxacin and amoxicillin/clavulanic acid in the treatment of 600 patients with AECB in a randomised, double-blind, multicentre study. The two drugs had comparable clinical cure rates (>90%), although the microbiological efficacy of the penicillin regimen was somewhat less.^[221] More recently, Wilson and coworkers^[216] compared the use of oral gemifloxacin

given once daily for 5 days with intravenous ceftriaxone followed by oral cefuroxime axetil (given for a maximum of 10 days) in the treatment of hospitalised patients with AECB. The clinical success rates at follow-up (21–28 days post-therapy) in the clinical per-protocol population were significantly higher for gemifloxacin than for ceftriaxone/cefuroxime (87% [105/121] for gemifloxacin versus 81% [91/112] for ceftriaxone/cefuroxime [treatment difference = 5.5; 95% CI -3.9, 14.9]). The corresponding clinical results in the intention-to-treat population were 82.6% (114/138) versus 72.1% (98/136), respectively (treatment difference = 10.5; 95% CI 0.7, 20.4). The safety of the two drug regimens

was also compared. There was no significant difference in the incidence or the type of adverse drug effects, and none of the patients in this study had a QTc interval change that was outside the normal range.^[216] In another open-label, noncomparative study, Ball et al.^[213] assessed the clinical and bacteriological efficacy of gemifloxacin in AECB and found that the drug had favourable clinical and bacteriological success rates. Sethi et al.^[217] studied oral gemifloxacin and oral levofloxacin in 360 adults in 60 medical centres in the US, UK and Germany, and found that the clinical response to both drugs was comparable.

Table VII. Results of clinical trials of gemifloxacin and comparator drugs for lower respiratory tract infections

Study	Design	Regimens	Organism eradication rate	Cure/improvement rate
Acute exacerbation of chronic bronchitis				
Wilson et al. ^[214] (GLOBE study)	r, db, mc	Gemifloxacin 320mg po od for 5 days	Overall, 87% (39/45)	85% (300/351)
		Clarithromycin 500mg po bid for 7 days	Overall, 73% (38/52)	85% (305/361)
File et al. ^[215]	r, db, mc	Gemifloxacin 320mg po od for 5 days	Overall, 91%	94%
		Amoxicillin/clavulanic acid 500mg/125mg po tid for 7 days	Overall, 80%	93%
Wilson et al. ^[216]	r, nb, c, mc	Gemifloxacin 320mg po od for 5 days	Overall, 81% (39/48)	87% (105/121)
		Ceftriaxone 1g IV od for 3 days then cefuroxime axetil 500mg po bid for 7 days	Overall, 82% (42/51)	81% (91/112)
Ball et al. ^[213]	nb, nc, mc	Gemifloxacin 320mg po od for 7 days	Overall, 91% (52/57)	83% (217/261)
Sethi et al. ^[217]	r, db, dd, mc, pl	Gemifloxacin 320mg po od for 7 days	ND	85% (155/182)
		Levofloxacin 500mg po od for 7 days		78% (139/178)
Community-acquired pneumonia				
Lode et al. ^[218]	r, nb, mc	Gemifloxacin 320mg po od for 7–14 days	Overall, 91% (58/64) <i>Streptococcus pneumoniae</i> , 90% (18/20) <i>Mycoplasma pneumoniae</i> , 100% (19/19) <i>Chlamydia pneumoniae</i> , 92% (12/13) <i>Haemophilus influenzae</i> , 86% (6/7) <i>Legionella pneumophila</i> , 100% (3/3)	92% (107/116)
		Ceftriaxone 2g IV od for 1–7 days then cefuroxime axetil 500mg po bid for 1–13 days	Overall, 87% (55/63) <i>S. pneumoniae</i> , 90% (17/19) <i>M. pneumoniae</i> , 93% (14/15) <i>C. pneumoniae</i> , 93% (14/15) <i>H. influenzae</i> , 92% (11/12) <i>L. pneumophila</i> , 100% (1/1)	93% (113/121)
Ball et al. ^[219]	nb, nc, mc	Gemifloxacin 320mg po od for 7 days	Overall, 78% (60/77)	83% (179/216)
Leophonte et al. ^[220]	r, mc, db, dd, pl	Gemifloxacin 320mg po od for 7 days	ND	89%
		Amoxicillin/clavulanate 1g/125mg tid for 10 days		88%

bid = twice daily; **c** = comparative; **db** = double-blinded; **dd** = double-dummy; **GLOBE** = Gemifloxacin Long term Outcomes of Bronchitis Exacerbation; **IV** = intravenous; **mc** = multicentre; **nb** = nonblind; **nc** = noncomparative; **ND** = no data; **od** = once daily; **pl** = parallel group; **po** = oral; **r** = randomised; **tid** = three times daily.

4.2.2 Community-Acquired Pneumonia

Zhanet al.^[59] reviewed the results of a study by File et al.^[222] comparing the efficacy of gemifloxacin with trovafloxacin in the treatment of CAP. This evaluation demonstrated similar efficacy, both clinically and microbiologically.^[59] Three more studies have subsequently been published examining the use of gemifloxacin for CAP (table VII). Lode and coworkers^[218] compared the use of oral gemifloxacin with sequential therapy with intravenous ceftriaxone and oral cefuroxime with or without a macrolide in the treatment of patients hospitalised with CAP in a randomised, open-label, multicentre study. The clinical and bacteriological efficacy of oral gemifloxacin were high and were comparable to the β -lactam regimen (with or without a macrolide).^[218] Ball and coworkers^[213] found that gemifloxacin achieved clinical and microbiological success in a subset of patients with CAP. Leophonte et al.^[220] randomised 324 patients with CAP in 102 medical centres in France, Poland and South Africa to either gemifloxacin orally each day for 7 days or amoxicillin/clavulanic acid orally for 10 days. The clinical cure rate in both groups was almost identical.

4.3 Gatifloxacin

4.3.1 Acute Exacerbation of Chronic Bronchitis

Zhanet al.^[59] reviewed an analysis by Ramirez and coworkers^[223] in which the results from two randomised, double-blind studies, and one non-blinded study evaluating the efficacy of gatifloxacin in the treatment of AECB were pooled. The clinical and bacteriological cure rates seen with gatifloxacin were comparable to either levofloxacin or cefuroxime axetil (91% vs 88% and 93% vs 88% for clinical and bacteriological cure, respectively).^[59,223] However, superior bacteriological eradication rates against *S. pneumoniae* and *H. influenzae* were seen with gatifloxacin (100% and 96%) versus its comparators (77% and 86%), respectively.^[59,224]

Three studies addressing the use of gatifloxacin in AECB have been published recently (table VIII). One group compared 5-day gatifloxacin, 7-day gatifloxacin and 10-day clarithromycin courses.^[225]

The short gatifloxacin course resulted in clinical cure rates comparable to those of the longer gatifloxacin and clarithromycin courses. The microbiological eradication rates were reported as >90% in all treatment groups. Another group assessed the efficacy and tolerability of gatifloxacin in an open-label, noncomparative, post-marketing trial. Overall clinical cure was demonstrated in up to 92% of patients.^[226] Nicholson et al.^[227] found a 90–93% clinical cure rate in patients with ages ranging from 18 to ≥ 80 years old.

4.3.2 Community-Acquired Pneumonia

Three randomised, double-blind trials comparing the efficacy of gatifloxacin to ceftriaxone (with or without erythromycin), clarithromycin or levofloxacin in patients with CAP have been reviewed previously.^[59] In these trials, gatifloxacin achieved slightly better clinical cure and bacteriological eradication rates (95% vs 91%), compared with its comparators (98% vs 93%), respectively.^[234-236] At least seven more studies addressing the use of gatifloxacin in CAP have since been published (table VIII). Franca and Carvalho,^[231] and Casillas and coworkers^[228] assessed the effectiveness, safety and tolerability of gatifloxacin in patients with CAP in two open-label, prospective, noncomparative, multicentre studies. Both demonstrated clinical cure rates of $\geq 95\%$. Nicholson et al.^[229] evaluated gatifloxacin in elderly patients and found good clinical success rates with *S. pneumoniae* infections (90%) as well as bacterial eradication rates (>94%). There was less of an effect (71%) in patients ≥ 80 years old.^[229] In another study reported by the same authors, clinical cure rates were >90% regardless of age.^[227] The bacteriological eradication rate (documented or presumed) was 95% for *S. pneumoniae*. No data were given for *H. influenzae*. Gotfried et al.^[208] reported the results from TeqCES, a community-based, open-label, prospective, noncomparative study of oral gatifloxacin use in outpatient CAP. The drug achieved clinical and microbiological cure rates of >90%. In two large trials, Lode et al.^[232,233] demonstrated the therapeutic equivalency of oral gatifloxacin with either clarithromycin or amoxicillin/clavulanic acid.

4.4 Moxifloxacin

4.4.1 Acute Exacerbations of Chronic Bronchitis

Two studies were recently reviewed in which moxifloxacin 400 mg/day was compared with clarithromycin for the treatment of AECB. The clinical success rates for moxifloxacin ranged from 89% to 95%, and the clinical success rates for clarithromycin ranged from 88% to 94%.^[59] Five studies have been published since this review comparing the efficacy of moxifloxacin and other agents (table IX). DeAbate et al.^[237] reported the results of a large clinical trial involving 37 centres in the US where moxifloxacin was compared with azithromycin. Both agents produced excellent eradication rates of key respiratory tract pathogens with correspondingly high clinical cure success rates. The authors concluded that a 5-day course of moxifloxacin was equivalent to azithromycin for AECB. Schaberg et al.^[238] reported the findings of a large trial involving 68 centres in 12 countries comparing moxifloxacin (one 400mg tablet daily for 5 days) therapy with that of amoxicillin/clavulanic acid (three 625mg tablets daily for 7 days). Overall, patients did well on either regimen.^[238] Miravittles and coworkers^[239] followed 5737 Spanish patients with ACEB on moxifloxacin and found that 93% of the assessable patients were cured after 1 week of therapy. The adverse effects were low (3.5%).^[239] In an Italian study, Grassi and coworkers^[240] found that oral daily moxifloxacin was equally efficacious to daily administration of intramuscular ceftriaxone. Therapeutic equivalency between moxifloxacin and amoxicillin/clavulanic acid was demonstrated by Starakis et al.^[241]

4.4.2 Community-Acquired Pneumonia

Two previously reviewed studies examined the efficacy of moxifloxacin 400 mg/day for the treatment of CAP.^[59] Clinical success rates were 93–95%. Five studies have been published since that review (table IX). Hammerschlag and Roblin^[242] attempted to assess the relative efficacy of moxifloxacin and clarithromycin in the treatment of CAP caused by *C. pneumoniae*. Unlike other studies, they defined infection on the basis of culture

rather than serology. Unfortunately, *C. pneumoniae* could be recovered from the nasopharyngeal secretions of only 19 (2.8%) of the 670 enrolled patients. Five additional patients were eliminated from the analysis because no follow-up cultures were done after treatment. Of the small number of patients treated, clarithromycin appeared to be more efficacious than moxifloxacin, although the numbers were too small for formal statistical comparison, and many of the patients were co-infected with *S. pneumoniae*, *H. influenzae* and other bacteria.^[242] Petitpretz and coworkers^[243] compared the efficacy of moxifloxacin and high-dose amoxicillin (3000 mg/day) in patients with CAP in a large study involving 82 centres in 20 countries. They found that both agents gave good results, although bacterial eradication rates and clinical cure rates were slightly higher with the fluoroquinolone. The frequency of adverse effects was also comparable in both groups.^[243] Another large, multinational, multicentre study was carried out by Hoeffken et al.^[244] to compare the efficacy of two doses of moxifloxacin (200 and 400 mg/day) with clarithromycin (500mg twice a day). All regimens were well tolerated with discontinuation rates of only 3–5%. The overall clinical cure rates were approximately 94% for all three regimens. The higher moxifloxacin dosage regimen was slightly superior in eradicating pathogens than were either of the other regimens.^[244]

Finch and coworkers^[245] examined the relative efficacies of moxifloxacin and a penicillin plus macrolide regimen for patients with CAP who were ill enough to require parenteral therapy. Intravenous moxifloxacin was switched to oral therapy as soon as possible after a mandatory 3-day period, and given for an additional 7–14 days. This regimen was compared to high-dose amoxicillin/clavulanic acid 1.2g, initially given intravenously for at least 3 days and then switched to oral administration. Clarithromycin could be added at the discretion of the treating physician to cover atypical pathogens, although these were diagnosed serologically in only 13.8% of the 326 patients enrolled. Overall, moxifloxacin therapy was superior to the penicillin plus macrolide regimen in terms of rates of clinical and bacteriolog-

Table VIII. Results of clinical trials of gatifloxacin and comparator drugs for lower respiratory tract infections

Study	Design	Regimens	Organism eradication rate	Cure/improvement rate
Acute exacerbation of chronic bronchitis				
Gottfried et al. ^[225]	r, p, db, mc	Gatifloxacin 400mg po od for 5 days	98% (85/87)	89% (135/151)
		Gatifloxacin 400mg po od for 7 days	94% (75/80)	88% (136/154)
		Clarithromycin 500mg po bid for 10 days	98% (87/89)	89% (145/163)
Nicholson et al. ^[227]	nc, mc	Gatifloxacin 400mg po od for 14 days	ND	90–93% depending upon age group (n = 2234)
Anzueto ^[226]	nb, nc	Gatifloxacin 400mg po od for 10 days	Overall, 94% (381/405) <i>Streptococcus pneumoniae</i> , 99% (73/74) <i>Haemophilus influenzae</i> , 96% (159/166) <i>Moraxella catarrhalis</i> , 89% (99/111)	92% (2084/2267)
Community-acquired pneumonia				
Casillas ^[228]	nb, nc, mc	Gatifloxacin 400mg po od for 7–14 days	ND	96% (3182/3322)
Nicholson et al. ^[229]	nc, mc	Gatifloxacin 400mg po od for 14 days	Overall >71% <i>S. pneumoniae</i> , 94–100% (n = 129) <i>H. influenzae</i> , 71–100% (n = 118)	Overall 92–96% depending upon age group (n = 1470)
Nicholson et al. ^[227]	nc, mc	Gatifloxacin 400mg po od for 14 days	<i>S. pneumoniae</i> , 95% (104/110) <i>S. pneumoniae</i> , 95% (117/123)	90–95% depending upon age group (n = 1469)
Gottfried et al. ^[230]	nb, nc, mc	Gatifloxacin 400mg po od for 7–14 days	Overall, 96% (282/295) <i>S. pneumoniae</i> , 95% (123/129) <i>H. influenzae</i> , 95% (112/118) <i>M. catarrhalis</i> , 98% (47/48)	95% (1417/1488)
Franca and Carvalho ^[231]	nb, nc, mc	Gatifloxacin 400mg po od for 7–14 days	ND	97% (1460/1501)
Lode et al. ^[232]	r, db, dd mc	Gatifloxacin 400mg po od for 5–14 days	Overall 95% (41/43) <i>S. pneumoniae</i> , 91% <i>H. influenzae</i> , 93% <i>M. catarrhalis</i> , 100% <i>Mycoplasma pneumoniae</i> , 100% <i>Chlamydophila pneumoniae</i> , 100%	92% (130/141)
		Clarithromycin 500mg po bid for 5–14 days	Overall 93% (43/46) <i>S. pneumoniae</i> , 82% <i>H. influenzae</i> , 95% <i>M. catarrhalis</i> , 100% <i>M. pneumoniae</i> , 100% <i>C. pneumoniae</i> , 100%	93% (135/145)
Lode et al. ^[233]	r, db, dd mc	Gatifloxacin 400mg po od for 5–10 days	Overall 86% (67/78) <i>S. pneumoniae</i> , 92% <i>H. influenzae</i> , 96% <i>M. catarrhalis</i> , 100%	87% (198/228)
		Amoxicillin/clavulanic acid 500mg/125mg po tid for 5–10 days	Overall 83% (78/94) <i>S. pneumoniae</i> , 100% <i>H. influenzae</i> , 84% <i>M. catarrhalis</i> , 90%	82% (186/228)

bid = twice daily; **db** = double-blinded; **dd** = double-dummy; **mc** = multicentre; **nb** = nonblind; **nc** = noncomparative; **ND** = no data; **od** = once daily; **p** = prospective; **po** = oral; **r** = randomised; **tid** = three times daily.

ical cure, time to resolution of fever (2 vs 3 days), the proportion of patients switching to oral therapy within 3 days (50% vs 18%) and length of hospital stay (9.5 vs 10.4 days).^[245] In a large trial that

involved 14 centres throughout the world, Torres et al.^[246] compared oral moxifloxacin with either amoxicillin or clarithromycin or both, given for 5–15 days. Seventeen percent of the comparator

group received amoxicillin alone, 24% received clarithromycin alone and 59% received both drugs. The clinical success rate of all tested regimens was approximately 94%. Moxifloxacin was better tolerated than the comparator regimens.^[246] The therapeutic equivalence of moxifloxacin and a combination of ceftriaxone, azithromycin and metronidazole for patients initially requiring intravenous therapy for CAP was shown by Katz and coworkers.^[247]

4.5 Summary of Clinical Trials

Overall, the newer fluoroquinolones often achieve clinical cure rates in $\geq 90\%$ of patients with AECB or CAP. Rates may be lower in HAP, but no clinical trials of gatifloxacin, gemifloxacin or moxifloxacin for nosocomial pneumonia have been published to date. No comparative clinical trials of any kind have been reported with garenoxacin. In the studies reviewed, there is little difference in the clinical success rates of the fluoroquinolones compared with the macrolides or β -lactams tested.

5. Adverse Drug Effects

The currently marketed US FDA-approved quinolones are considered to be relatively safe and well tolerated. However, like any other class of drugs, adverse effects may be encountered (table X).^[248,249] Gastrointestinal and CNS effects are the most frequent adverse events.^[55,250,251]

5.1 Gastrointestinal

Gastrointestinal adverse effects include altered taste, anorexia, nausea, vomiting and diarrhoea. These effects range in incidence from 2–20% according to the quinolone used and are most common with trovafloxacin.^[55,64,251] The overall rates among the newer fluoroquinolones is similar (1–3%), although nausea, vomiting and diarrhoea may be higher with moxifloxacin and gatifloxacin compared with levofloxacin.^[248]

5.2 CNS

CNS adverse effects include dizziness, headache, somnolence and, less commonly, agitation, deliri-

um, confusion, psychosis, abnormal vision and, rarely, seizures. Seizures may be encountered more often when quinolones are used to treat patients with a history of strokes or seizure disorders, and in patients in whom potentially epileptogenic medications such as NSAIDs or theophylline are concomitantly administered. CNS adverse effects have an overall incidence of 1–2%, and are most common with trovafloxacin and least common with levofloxacin and gemifloxacin.^[55,64,251]

5.3 Dermatological

Dermatological adverse effects include rash, pruritus, photosensitivity, hyperpigmentation and urticaria. Phototoxicity has been linked primarily to the presence of a halogen atom at the C8 position of the quinolone nucleus in compounds such as sparfloxacin and clinafloxacin. Substitution of methyl groups at the C8 position, as in gatifloxacin and moxifloxacin, has significantly reduced the phototoxic potential. The dermatological adverse effects range in incidence from 0.05% to 19%, being seen most often with clinafloxacin and sparfloxacin (which were taken off the market), and least often with trovafloxacin, gatifloxacin and moxifloxacin.^[55,64,251] The recently US FDA-approved fluoroquinolone, gemifloxacin, has a 2.8% incidence of rash which occurs more commonly among women under 40 years of age.^[199]

5.4 Musculoskeletal

Musculoskeletal adverse effects include arthropathy, chondrotoxicity, tendonitis and tendon rupture. Arthropathy and chondrotoxicity have mainly been shown in immature laboratory animals, and seem to be very rare in humans, perhaps because of limited use of these agents among children. However, arthralgias or arthritis has been reported to occur with an incidence of 1–1.5% in children and juveniles treated with ciprofloxacin.^[252,253] On the other hand, there are case reports of tendonitis and rupture of the Achilles tendon with the use of ciprofloxacin, ofloxacin, norfloxacin and levofloxacin.^[55,64,254,255] Risk factors for tendinopathy include renal failure and corticosteroid use.^[256]

Table IX. Results of clinical trials of moxifloxacin and comparator drugs for lower respiratory tract infections

Study	Design	Regimens	Organism eradication rate	Cure/improvement rate
Acute exacerbation of chronic bronchitis				
DeAbate et al. ^[237]	p, r, db, mc	Moxifloxacin 400mg po od for 5 days	Overall, 91% (106/116) <i>Streptococcus pneumoniae</i> , 100% <i>Haemophilus influenzae</i> , 100% <i>Moraxella catarrhalis</i> , 100%	91% (192/212)
		Azithromycin 500mg po for 1 day, then 250mg for 4 days	Overall, 90% (104/115) <i>S. pneumoniae</i> , 100% <i>H. influenzae</i> , 92% <i>M. catarrhalis</i> , 100%	92% (208/227)
Schaberg et al. ^[238]	r, mc	Moxifloxacin 400mg po od for 5 days	Overall, 88% (64/73)	96% (251/261)
		Amoxicillin/clavulanic acid 500mg/125mg tid for 7 days	Overall, 90% (60/67)	92% (230/251)
Miravittles et al. ^[239]	mc, nc	Moxifloxacin 400mg po od for 5 days	ND	93% (4613/4957)
Grassi et al. ^[240]		Moxifloxacin 400mg po od for 5 days	Overall, 92% (33/36)	91%
		Ceftriaxone 1g IM od for 7 days	Overall, 93% (28/30)	89%
Starakis et al. ^[241]	r, nb	Moxifloxacin 400mg po od for 5 days	Overall, 91% (20/22)	89% (70/79)
		Amoxicillin/clavulanic acid 500mg/125mg tid for 7 days	Overall, 90% (18/20)	89% (66/74)
Community-acquired pneumonia				
Hammerschlag and Roblin ^[242]	r, db	Moxifloxacin 400mg po od for 10 days	<i>Chlamydomphila pneumoniae</i> , 70% (7/10)	100% (10/10)
		Clarithromycin 500mg po bid for 10 days	<i>C. pneumoniae</i> , 100% (4/4)	100% (4/4)
Petitpretz et al. ^[243]	r, db, mc	Moxifloxacin 400mg po od for 10 days	Overall, 90% (63/70) <i>S. pneumoniae</i> , 90% <i>H. influenzae</i> , 100%	92% (162/177)
		Amoxicillin 1000mg po tid for 10 days	Overall, 83% (65/78) <i>S. pneumoniae</i> , 85% <i>H. influenzae</i> , 83%	90% (166/185)
Hoeffken et al. ^[244]	r, p, db, mc	Moxifloxacin 200mg po od for 10 days	Overall, 69% (24/35) <i>S. pneumoniae</i> , 95% <i>H. influenzae</i> , 100% <i>M. catarrhalis</i> , 0% <i>C. pneumoniae</i> , 87% <i>Mycoplasma pneumoniae</i> , 93%	94% (169/180)
		Moxifloxacin 400mg po od for 10 days	Overall, 79% (37/47) <i>S. pneumoniae</i> , 91% <i>H. influenzae</i> , 100% <i>M. catarrhalis</i> , 80% <i>C. pneumoniae</i> , 95% <i>M. pneumoniae</i> , 93%	94% (167/177)
		Clarithromycin 500mg po bid for 10 days	Overall, 66% (23/35) <i>S. pneumoniae</i> , 92% <i>H. influenzae</i> , 70% <i>M. catarrhalis</i> , 100% <i>C. pneumoniae</i> , 94% <i>M. pneumoniae</i> , 94%	94% (164/174)

Continued next page

Table IX. Contd

Study	Design	Regimens	Organism eradication rate	Cure/improvement rate
Finch et al. ^[245]	r, p, mc	Moxifloxacin 400mg IV for ≥ 3 days followed by oral for 7–14 days	Overall, 94% (60/64) <i>S. pneumoniae</i> , 100% <i>H. influenzae</i> , 100% <i>C. pneumoniae</i> , 100% <i>M. pneumoniae</i> , 100%	93% (241/258)
		Amoxicillin/clavulanic acid 1.2g IV tid for ≤ 3 days followed by 625mg po tid for 7–14 days \pm clarithromycin 500mg IV or po bid	Overall, 82% (58/71) <i>S. pneumoniae</i> , 77% <i>H. influenzae</i> , 89% <i>C. pneumoniae</i> , 80% <i>M. pneumoniae</i> , 94%	85% (239/280)
Torres et al. ^[246]	r, mc	Moxifloxacin 400mg po od for 10 days	ND	94% (201/215)
		Amoxicillin 1g po tid or clarithromycin 500mg po bid or a combination of the two for 5–15 days	ND	94% (217/231)
Katz et al. ^[247]	r, mc	Moxifloxacin 400mg IV od then switch to po	Overall, 80% (8/10) <i>S. pneumoniae</i> , 86% <i>H. influenzae</i> , 67%	83% (90/108)
		Ceftriaxone 2g IV \pm azithromycin 500mg IV od \pm metronidazole 500mg IV every 6 hours then switch to cefuroxime 500mg po bid \pm azithromycin 250mg po od \pm metronidazole 500mg po every 6 hours	Overall, 69% (9/13) <i>S. pneumoniae</i> , 78% <i>H. influenzae</i> , 50%	80% (90/113)

bid = twice daily; **db** = double-blinded; **IM** = intramuscular; **IV** = intravenous; **mc** = multicentre; **nb** = nonblind; **nc** = noncomparative; **ND** = no data; **od** = once daily; **p** = prospective; **po** = oral; **r** = randomised; **tid** = three times daily.

5.5 Cardiovascular

The fluoroquinolones can cause hypotension, tachycardia and prolongation of the QTc interval.^[257] The latter effect, although rarely encountered, may lead to cardiac arrhythmias in patients with hypokalaemia, underlying heart disease, or in those who are receiving antiarrhythmic drugs that prolong the QTc interval such as quinidine, procainamide, disopyramide, sotalol or amiodarone. A recent double-blinded, randomised, four-period, four-treatment, four-sequence, crossover trial compared the effect of placebo, levofloxacin 1000mg, moxifloxacin 800mg and ciprofloxacin 1500mg on QTc interval prolongation. The drug doses were twice that recommended by the US FDA for routine clinical use. Increases in QT or QTc interval compared with placebo were statistically significant for all three antibacterials and were consistently greater with moxifloxacin (16.34–17.83ms over placebo) than with either levofloxacin (3.53–4.88ms) or ciprofloxacin (2.27–4.93ms). However, no adverse effects were experienced by any of the volunteers in

the study.^[258] In another study, Demolis and co-workers^[259] compared the effect of moxifloxacin 400mg and 800mg versus placebo on the QTc interval of 18 healthy men and women in a double-blind, randomised, placebo-controlled, crossover study. ECGs were recorded at rest and with exercise. There was a $2.3\% \pm 2.8\%$ and $4.5\% \pm 3.8\%$ (mean \pm SD) increase relative to placebo for the two doses across a wide range of RR intervals. Although these changes were statistically significant, the authors concluded that the risk of moxifloxacin-induced torsades de pointes would be low with moxifloxacin 400mg. However, they advised caution when using the drug in patients with predisposing factors for torsades de pointes such as electrolyte disturbances and bradycardia, or during coadministration of proarrhythmic drugs.^[259] QTc interval prolongation has also been reported with sparfloxacin and grepafloxacin, both of which have been removed from the market.^[55,64,72,260-262]

Blood pressure changes including hypertension, hypotension and postural hypotension have been

Table X. Adverse drug effects of quinolone antibacterials [192,194,195,197,199]

Drug	Gastrointestinal	CNS	Dermatological	Musculoskeletal	Cardiovascular	Idiosyncratic reactions
Norfloxacin	±	+	+	±	ND	ND
Ciprofloxacin	+	+	+	+	±	±
Levofloxacin	±	±	+	±	±	±
Gatifloxacin	++	+	±	±	±	±
Moxifloxacin	++	+	±	±	+	+
Gemifloxacin	±	±	++	ND	±	ND

ND = no data; ±, +, ++ indicate relative incidence (lowest to highest).

reported in an incidence of <1% with the use of the currently marketed quinolones.^[192,194,195,197,199] Histamine release has been postulated as one of the responsible mechanisms for hypotension.^[263] Severe hypotension may occur after a single dose of the currently restricted quinolone trovafloxacin.^[260] As mentioned in section 1.4, hypotension has occurred more with the new quinolone garenoxacin than its comparators in phase III trials.

5.6 Glucose Metabolism

Gatifloxacin has been shown to have no marked effect on glucose tolerance or pancreatic β -cell function. However, it did cause a brief increase in serum insulin levels.^[264] Severe and persistent hypoglycaemia caused by gatifloxacin interactions with oral hypoglycaemic agents were reported in at least three case reports.^[265] Ciprofloxacin may also cause slight fluctuations in blood sugar levels in patients receiving oral hypoglycaemic drugs.^[266]

5.7 Idiosyncratic Reactions

There have been reports of asymptomatic and symptomatic hepatitis, pancreatitis, severe hepatotoxicity and death associated with trovafloxacin. As noted earlier, the US FDA has advised restricting the use of this drug to patients with life- or limb-threatening infections. Clinicians are advised to monitor serum transaminases and other indices of hepatobiliary function in patients receiving hepatically metabolised quinolones such as trovafloxacin and moxifloxacin.^[64,72,260]

5.8 Summary of Adverse Drug Effects

In summary, the currently marketed fluoroquinolones appear to be a safe and well tolerated class of drugs, although several compounds have either been withdrawn from the market (temafloxacin), restricted (trovafloxacin) or never released (sparfloxacin, grepafloxacin and perhaps garenoxacin). The most common adverse effects are gastrointestinal but the overall rate is low (1–3%). Discontinuation rates among the newer fluoroquinolones are about the same.^[248] Perhaps the adverse effect of most concern is prolongation of the QTc interval since this can lead to dangerous arrhythmias. Prolongation appears to be greatest with moxifloxacin. Unfortunately, there is no known threshold for QT interval prolongation above which arrhythmias will occur and below which it is known to be safe.^[249] It is known that in post-marketing trials of ciprofloxacin and levofloxacin, arrhythmias occurred at a rate of less than one per million patients.^[190] Whether this rate will be higher with gatifloxacin, gemifloxacin and moxifloxacin will only be known after the drugs are used more extensively. Of interest, QTc interval prolongation has been reported with a number of other antimicrobials including the macrolides and imidazoles.^[267]

6. Important Drug Interactions

Other drugs may alter serum fluoroquinolone concentrations, or the fluoroquinolones may alter their metabolism.

6.1 Drugs Affecting Serum Fluoroquinolone Concentrations

Multivalent cations such as iron, zinc, calcium, aluminium and magnesium may form insoluble complexes with orally administered fluoroquinolones in the gastrointestinal tract and decrease the absorption of the antibacterial by >90%. Examples of these drugs include multivitamins and mineral supplements, antacids and sucralfate. When these drugs are necessary, they should be administered at least 4 hours before or 2 hours after oral administration of a fluoroquinolone to avoid interactions. The antiretroviral drug didanosine also impairs the absorption of quinolones because the drug formulation contains calcium carbonate and magnesium hydroxide buffers.^[65,250,268,269] Probenecid, loop diuretics and cimetidine increase serum fluoroquinolone concentrations.^[192,194,195,197,199]

6.2 Drugs Affected by Fluoroquinolones

The quinolones inhibit the cytochrome P450 system leading to increased serum concentrations of drugs such as theophylline, caffeine, digoxin, ciclosporin (cyclosporin) and warfarin. Newer fluoroquinolones such as levofloxacin, gatifloxacin and moxifloxacin have less of an effect on theophylline pharmacokinetics than older agents. Fluoroquinolones should be used with caution in patients receiving Class Ia (procainamide, quinidine, disopyramide) and Class III (amiodarone, bretylium, sotalol, dofetilide, ibutilide) antiarrhythmic drugs, as well as erythromycin, cisapride, antipsychotics and tricyclic antidepressants that prolong the QTc interval, because of the increased potential for fatal tachyarrhythmias.^[63,65,268] Concurrent use of corticosteroids may increase the risk of tendon rupture, especially in elderly patients.^[192,194,195,197,199] Some fluoroquinolones, such as gatifloxacin and to a lesser extent ciprofloxacin, interact with oral hypoglycaemic agents which may result in serious hypoglycaemia.^[265,266]

7. Role of Fluoroquinolones in Clinical Practice

7.1 Acute Bronchitis

The use of antibacterials in acute bronchitis is discouraged because the aetiology is most often viral.^[5] The use of antibacterials in this syndrome results in unnecessary costs, adverse drug effects and the potential for selection of resistant bacteria.^[3,4] Further clinical evaluation, radiographic imaging and microbiological studies should be carried out for those patients with presentations suggesting more serious illness such as pneumonia or in those with severe or prolonged duration of illness.^[1] Antibacterials may be used if an underlying bacterial aetiology is found. In this case, a macrolide or a tetracycline may be appropriate.^[5] Fluoroquinolones should be reserved as second-line agents for patients with resistant bacteria. Following local trends in antibacterial resistance may be of value.

7.2 Acute Exacerbation of Chronic Bronchitis

Several guidelines addressing the management of AECB have been published.^[8,270-273] Stratification of patients allows identification of patients who are at high risk for infection with resistant bacteria, treatment failure and a complicated course. High-risk factors include significant impairment of lung function with an FEV₁ of <50%, four or more episodes of AECB per year, oral corticosteroid use, age >65 years and co-morbid conditions such as diabetes mellitus, heart disease or renal failure. In these patients, an aggressive approach including sputum Gram-stain and cultures, and the initial, empirical use of broad-spectrum antibacterials is justified to avoid treatment failure.^[8,271,273]

When deciding whether to use a fluoroquinolone or an alternative class of antibacterial for patients with AECB, it is helpful to have information on local bacterial resistance rates. Unfortunately, data are often available only from large national (or international) surveys and may differ depending upon the source of the isolates (hospital vs community). For instance, in one large study of hospital

isolates collected in the US during the 1999–2000 respiratory season, more than 30% of *H. influenzae* strains were resistant to ampicillin and 14% were resistant to co-trimoxazole. Less than 1% of the isolates were resistant to either clarithromycin or azithromycin. A full 34% of the *S. pneumoniae* isolates were non-susceptible (intermediate plus resistant) to penicillin, and this varied by geographic region (ranging from 44% in the South Atlantic to 24% in New England).^[140] A study of isolates collected from 2795 primary care providers in the US showed that penicillin non-susceptibility among *S. pneumoniae* was about the same (33%), but up to 7.3% of the *H. influenzae* isolates were resistant to clarithromycin.^[40] In another study of *S. pneumoniae* isolates collected in 1999–2000, intermediate and resistant rates were 34.2% for penicillin, 26.2% for the macrolides, 35.9% for co-trimoxazole and 16.6% for tetracycline.^[139]

COPD patients with AECB and no high-risk factors are usually treated on an outpatient basis. In this setting, sputum Gram-stain and culture do not seem to be cost effective and are not recommended.^[272,274] In our opinion, amoxicillin/clavulanic acid or newer macrolides such as clarithromycin or azithromycin should be used as first-line therapy and fluoroquinolones reserved as second-line agents. Data showing recent *in vitro* trends in macrolide resistance among *S. pneumoniae* and clinical failures with these agents are of concern.^[40,140,156,275-277] However, controversies about the relevance of *in vitro* data to clinical outcomes,^[278,279] and the lack of superior outcomes when fluoroquinolones are compared with the newer macrolides or β -lactam/ β -lactamase combinations in clinical studies (see tables VI to IX) suggest that the latter agents can still be used successfully.

High-risk patients with AECB are usually treated in the hospital setting. In these patients, sputum Gram-stain and cultures are cost effective because they help in directing antibacterial therapy. This is because these patients are often at risk for infection with antibacterial-resistant enteric Gram-negative bacteria and *P. aeruginosa*. Empirical therapy may be started with an intravenous third- or fourth-gener-

ation cephalosporin (e.g. ceftazidime or cefepime) and an aminoglycoside if *P. aeruginosa* is suspected, until sputum culture results and antibacterial sensitivity data are available.^[271,272,274] One author suggested that fluoroquinolone monotherapy provides good clinical outcomes, higher quality of life and lower costs in this setting.^[8]

7.3 Community-Acquired Pneumonia

The IDSA recently published guidelines for the management of CAP and provided recommendations for choosing antimicrobial therapy. These recommendations include pathogen-specific treatment for cases in which an aetiological diagnosis is established, and empirical treatment for patients in whom an aetiological diagnosis is not known. Whenever an aetiological organism is determined, changing to the antimicrobial agent that is most cost effective, least toxic and has the most narrow spectrum is encouraged.^[26] Recommendations for treating patients who require empirical antibacterial selection are based on the likely pathogen, local resistance patterns, comorbid conditions, the severity of illness and the site of care. It was recommended that a decision to hospitalise the patient should be based on an assessment of pre-existing conditions that may compromise the safety of the patient if they are sent home; a PORT (Pneumonia Outcomes Research Team) Severity Index (PSI) score greater than class III, and clinical judgment. Although there was concern that misuse and overuse of fluoroquinolones could lead to increasing pneumococcal resistance and more clinical failures, the use of fluoroquinolones alone was recommended in several instances (table XI).

The American Thoracic Society (ATS) guidelines for the management of CAP have also included recommendations on choosing antimicrobial therapy (table XI).^[39] As with the IDSA guidelines, the ATS recommendations are based on patient stratification according to site of care (outpatient, inpatient ward or intensive care unit [ICU]), the presence of cardiopulmonary disease and the presence of 'modifying factors'. Modifying factors define clinical settings that place the patient at risk for infection with

Table XI. Comparison of Infectious Diseases Society of American (IDSA) and the American Thoracic Society (ATS) recommendations for empirical treatment of community-acquired pneumonia

IDSA recommendations, 2003 ^[26]	ATS recommendations, 2001 ^[39]
Outpatient	
Previously healthy with no recent antibacterial therapy → a macrolide ^a or doxycycline Previously healthy with antibacterial therapy within the last 3 months → a respiratory fluoroquinolone ^b alone, an advanced macrolide ^c + high-dose amoxicillin (1g tid), or an advanced macrolide plus high-dose amoxicillin/clavulanic acid (2g bid) Comorbidities ^d and no recent antibacterial therapy → an advanced macrolide or a respiratory fluoroquinolone Comorbidities and recent antibacterial therapy → a respiratory fluoroquinolone alone or an advanced macrolide + a β-lactam ^e Suspected aspiration with infection → amoxicillin/clavulanic acid or clindamycin Influenza with bacterial superinfection → a β-lactam ^e or a respiratory fluoroquinolone	No cardiopulmonary disease and no modifying factors ^f → an advanced macrolide ^c or doxycycline Cardiopulmonary disease and/or modifying factors ^f → a β-lactam ^g + an advanced macrolide or doxycycline/ <i>or</i> → a respiratory fluoroquinolone alone
Inpatient ward	
No recent antibacterial therapy → a respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam ^h Recent antibacterial therapy → an advanced macrolide + a β-lactam ^h or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibacterial therapy)	Cardiopulmonary disease and/or modifying factors → an IV β-lactam ⁱ + po or IV advanced macrolide ^c or doxycycline/ <i>or</i> → an IV respiratory fluoroquinolone alone No cardiopulmonary disease or modifying factors → an IV advanced macrolide ^c alone <i>or</i> → an IV β-lactam + po or IV advanced macrolide ^c or doxycycline/ <i>or</i> → an IV respiratory fluoroquinolone alone
Inpatient ICU	
Pseudomonal infection unlikely → a β-lactam ^h + either an advanced macrolide or a respiratory fluoroquinolone Pseudomonal infection unlikely but patient has a β-lactam allergy → a respiratory fluoroquinolone, with or without clindamycin Pseudomonal infection likely ^j → either: (i) an antipseudomonal agent ^k + ciprofloxacin; or (ii) an antipseudomonal agent + an aminoglycoside + a respiratory fluoroquinolone or a macrolide Pseudomonal infection likely but the patient has a β-lactam allergy → either: (i) aztreonam + levofloxacin; or (ii) aztreonam + moxifloxacin or gatifloxacin, with or without an aminoglycoside	No risk factors for Pseudomonal infection → an IV β-lactam ⁱ + an IV advanced macrolide ^c or an IV respiratory fluoroquinolone Risk factors for Pseudomonal infection → either: (i) an antipseudomonal agent ^k + ciprofloxacin; or (ii) an antipseudomonal agent + an aminoglycoside + a respiratory fluoroquinolone or a macrolide
Nursing home patient	
Receiving treatment in nursing home → a respiratory fluoroquinolone alone or amoxicillin/clavulanic acid + an advanced macrolide Hospitalised → same as for medical ward and ICU	No particular recommendations
<p>a Erythromycin, azithromycin or clarithromycin.</p> <p>b Moxifloxacin, gatifloxacin, levofloxacin or gemifloxacin (gemifloxacin is only available orally).</p> <p>c Azithromycin, or clarithromycin.</p> <p>d Chronic obstructive pulmonary disease, diabetes mellitus, renal or congestive heart failure or malignancy.</p> <p>e High-dose amoxicillin, high-dose amoxicillin/clavulanic acid, cefpodoxime, cefprozil or cefuroxime.</p> <p>f See text section 7.3.</p> <p>g Selected oral β-lactam antibacterials include oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanic acid.</p> <p>h Cefotaxime, ceftriaxone, ampicillin-sulbactam or ertapenem; ertapenem was recently approved for such use (in once-daily parenteral treatment) but there is little experience thus far.</p> <p>i Selected IV β-lactam antibacterials include cefotaxime, ceftriaxone, ampicillin/sulbactam. ATS-defined risk factors for infection with <i>Pseudomonas aeruginosa</i> include any of the following: structural lung disease (bronchiectasis), antibacterials for >7 days in the past month, corticosteroid therapy with >10 mg/day of prednisone or malnutrition.</p> <p>j Risk factors for Pseudomonal infection include severe structural lung disease (e.g. bronchiectasis), and recent antibacterial therapy or stay in hospital (especially in the ICU).</p> <p>k Piperacillin, piperacillin-tazobactam, imipenem, meropenem or cefepime.</p>	
<p>bid = twice daily; ICU = intensive care unit; IV = intravenous; po = oral; tid = three times daily.</p>	

drug resistant *S. pneumoniae*, enteric Gram-negative bacteria or *P. aeruginosa*. Risk factors for infection with drug-resistant *S. pneumoniae* include age >65 years, β -lactam therapy in the past 3 months, alcoholism, immunosuppressive illness (including corticosteroid therapy, but not HIV infection), multiple medical comorbidities and exposure to a child in a daycare centre. Risk factors for infection with enteric Gram-negative bacteria include residence in a nursing home, underlying cardiopulmonary disease, multiple medical co-morbidities and recent antibacterial therapy. Risk factors for infection with *P. aeruginosa* include structural lung disease (bronchiectasis), antibacterial therapy for more than 7 days in the past month, corticosteroid therapy at the equivalent of >10 mg/day of prednisone and malnutrition. Recommended antibacterial regimens are given in table XI. As with the IDSA guidelines, fluoroquinolones were often recommended as single agents.

Other organisations have made recommendations for the treatment of CAP. The CDC, focusing primarily on drug-resistant *S. pneumoniae* (defined as an MIC $\geq 4\mu\text{g/mL}$) recommended an oral β -lactam plus a macrolide or tetracycline, even if pneumococcal resistance was a concern. An intravenous β -lactam plus a macrolide was recommended for empirical therapy of hospitalised patients with CAP. The CDC emphasised that fluoroquinolones should not be used routinely to treat CAP, but should be reserved for those patients who have failed other regimens or who have documented high-level, drug-resistant *S. pneumoniae*.^[280] In contrast to the American recommendations, the Canadian guidelines call for a 'respiratory' fluoroquinolone as the first choice for all persons admitted to hospital.^[281]

7.4 Hospital-Acquired Pneumonia

The ATS guidelines for management of HAP are based on the time of onset during hospitalisation, disease severity and the presence of risk factors for specific organisms.^[47] It is recommended that HAP beginning on the third or fourth day of hospitalisation be treated as CAP (see section 7.3). In contrast, it is recommended that HAP encountered on the

fifth day of hospitalisation or later should be assumed to be a result of organisms acquired in the hospital and treated accordingly.

Empirical, early and adequate antibacterial therapy based on the knowledge of the most likely infecting organisms has been shown to reduce morbidity and mortality in HAP.^[47,282-285] The ATS defines pathogens that are the most likely aetiologies for HAP in the absence of specific risk factors (see below). These bacteria include *E. coli*, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Serratia marcescens*, *H. influenzae*, methicillin-sensitive *S. aureus* and *S. pneumoniae*. Risk factors for additional pathogens include witnessed aspiration, recent abdominal surgery, coma, head trauma, recent influenza, history of intravenous drug use, diabetes, renal failure, high-dose corticosteroids, prolonged ICU stay, structural lung disease, antibacterial use before the onset of pneumonia and prolonged mechanical ventilation. The presence of these risk factors increases the probability of infections due to *P. aeruginosa*, *Acinetobacter* spp., MRSA, anaerobes and *Legionella* spp.^[47]

For the initial empirical therapy for HAP or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens and of early onset, the ATS recommends monotherapy with a ceftriaxone, ampicillin/sulbactam, ertapenem or a quinolone (ciprofloxacin, levofloxacin or moxifloxacin). For patients with late onset disease or risk factors for multidrug-resistant bacteria, the ATS recommends that patients be treated with an antipseudomonal cephalosporin (cefepime or ceftazidime), or an antipseudomonal carbapenem (imipenem/cilastin or meropenem), or a β -lactam/ β -lactamase inhibitor combination (piperacillin/tazobactam), plus an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside. Linezolid or vancomycin should be used when MRSA is suspected.^[47]

Studies on the use of fluoroquinolones in HAP mainly involved the use of ciprofloxacin.^[286-288] One study showed equivalence of high-dose levofloxacin with imipenem/cilastatin followed by oral ciprofloxacin (table VI),^[212] but the use of other newer fluoro-

quinolones such as gatifloxacin and moxifloxacin has not been evaluated in this setting. While ciprofloxacin remains the most active quinolone against *P. aeruginosa* *in vitro*, levofloxacin may be as effective in the clinical setting, given its superior pharmacokinetics.^[68-70] Despite activity against *P. aeruginosa*, however, use of a fluoroquinolone as monotherapy in HAP cannot be justified, since high clinical failure rates and the evolution of resistance in *P. aeruginosa* have been observed with ciprofloxacin monotherapy.^[286,287] Fluoroquinolones may be used as an alternative to an aminoglycoside in combination with an antipseudomonal β -lactam when there are concerns about renal dysfunction. These drugs are not reliably synergistic with β -lactams against *P. aeruginosa* as are the aminoglycosides.^[289,290]

8. Conclusion

Newer fluoroquinolones such as levofloxacin, moxifloxacin, gatifloxacin and gemifloxacin have several attributes that make them good choices for the therapy of lower respiratory tract infections. They have excellent intrinsic activity against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and the atypical respiratory pathogens; their pharmacokinetics allows single daily dose administration, and they are generally well tolerated and have a good safety profile. Clinical trials have shown that they achieve high microbiological eradication and clinical success rates, and they compare favourably with β -lactams and the newer macrolides. Unfortunately, bacteria can become resistant to these agents through a series of simple spontaneous mutations. Numerous studies ranging from *in vitro* experiments to case reports, and large surveillance databases have shown that resistance can, and does, occur. Currently, the overall prevalence of resistance to the newer fluoroquinolones is low, but this is not necessarily reassuring. As Austin et al. pointed out, there is typically a long period of very low-level resistance that precedes a rapid increase in resistance.^[291] This has been the case with MRSA, vancomycin-resistant *Enterococci* and penicillin-resistant *S. pneumoniae*. The recently reported

increased prevalence of levofloxacin resistance among pneumococcal isolates collected from across the US, with figures exceeding 4.6% in certain states such as Massachusetts and Colorado, is very worrisome.^[144] Of greater concern is cross-resistance among fluoroquinolones. This has clearly been shown to occur when pathogens are exposed to older, less potent agents that select single-step, low-level resistant mutants. These mutants may have decreased susceptibility to newer fluoroquinolones, and may acquire high-level resistance with additional mutations in a second target gene. Because of this, some investigators have suggested that less potent fluoroquinolones (ciprofloxacin and levofloxacin) be abandoned in favour of more potent ones (gatifloxacin, moxifloxacin or gemifloxacin) for the treatment of CAP in an effort to prevent class resistance.^[39,56,58,114,236,292,293] Clinical failures have been documented with ciprofloxacin leading the US FDA to suggest that the drug not be used for lower respiratory tract infections caused by *S. pneumoniae*. It is of interest that a similar number of levofloxacin failures have also been reported but no such recommendations have been forthcoming. Theoretically, ciprofloxacin would be expected to be less efficacious for infections caused by *S. pneumoniae* because its pharmacodynamic ratios are <20% of the newer agents (table V). The pharmacodynamic ratios of levofloxacin and gatifloxacin are <60% of those of moxifloxacin or gemifloxacin. Whether this will make a difference in patient outcomes remains to be seen. Data published from recent clinical trials involving levofloxacin, gatifloxacin, moxifloxacin and gemifloxacin suggest that there is little difference among these fluoroquinolones in the eradication rates of *S. pneumoniae* (tables VI to IX).

An approach, originally recommended for conservation of β -lactam efficacy against *S. pneumoniae*, also seems appropriate for the fluoroquinolones. This approach entails: (i) reduction of prescribing of drugs whose consumption correlates strongly with resistance; (ii) development of new formulations or administration strategies to deal with resistant strains; and (iii) use of antibacterials with the maximal capacity for bacterial eradication.^[294] In our

opinion, ciprofloxacin should not be used for lower respiratory tract infections. Of concern is the newly released Cipro[®] XR.¹ This formulation consists of a bilayer matrix. The first layer releases ciprofloxacin into serum and tissues within hours, while the second layer releases the drug more slowly, allowing sustained levels over 24 hours.^[295] Peak concentrations achieved with the extended-release formulation are approximately 50% of those achieved with administration of the conventional formulation. Cipro[®] XR 500mg has been approved by the US FDA solely for once-daily treatment of urinary tract infections.^[296] We are concerned that exposure of patients to low, sustained concentrations of ciprofloxacin may unintentionally select resistant *S. pneumoniae* colonising the respiratory tract and that extensive use of this product may rapidly accelerate class resistance to the fluoroquinolones. This situation would be exacerbated if clinicians opt for Cipro[®] XR when treating AECB or CAP because of its convenience.

In our opinion, the key to eradicating respiratory pathogens and preserving fluoroquinolones as a class is to focus on eradicating low-level resistant, minor subpopulations of bacteria that often exist in an infection. To this end, optimising the AUC₂₄/MPC or C_{max}/MPC ratio is important. In our opinion, agents such as moxifloxacin and gemifloxacin with high ratios are preferred, and agents such as ciprofloxacin with low ratios should be avoided. For agents such as levofloxacin and gatifloxacin, with intermediate ratios, it may be worthwhile to consider alternative dose administration strategies. This could involve using higher doses throughout a course of therapy, or the approach suggested by Champion et al. where a single large dose is initially administered to eradicate low-level resistant variants, followed by a standard administration regimen to kill the sensitive majority.^[187] In our opinion, it would be of value to test these approaches in further *in vitro* experiments as well as clinical trials.

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1 The use of trade names is for product identification purposes only and does not imply endorsement.

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- Correspondence and offprints: Dr *Martin E. Evans*, Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine, Room MN 672, 800 Rose Street, Lexington, KY 40536, USA.
E-mail: Martin.Evans@uky.edu