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## The new fluoroquinolones: A critical review

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The birth of the fluoroquinolones as a class of antibiotics dates back to the discovery of nalidixic acid in the early 1960s ([1](#)). Nalidixic acid demonstrated activity against Gram-negative bacilli, such as *Escherichia coli*, *Klebsiella* species and *Proteus* species, was well absorbed following oral administration and produced high concentrations in urine ([2,3](#)). Unfortunately, there were several problems limiting its use. These included frequent daily administration (four times daily), a high tendency to select for resistant Gram-negative bacilli, poor activity against Gram-positive bacteria, photosensitivity reactions in patients and the potential to cause convulsions in patients with seizure disorders ([2–5](#)).

The introduction of norfloxacin followed by ciprofloxacin (Cipro, Bayer Healthcare Division) in the mid-1980s was a major advancement over nalidixic acid. Ciprofloxacin demonstrated excellent activity against Gram-negative bacilli and displayed

some activity against Gram-positive bacteria. The pharmacokinetic profile of ciprofloxacin allowed for twice daily dosing. Ciprofloxacin's ability to achieve high concentrations in various tissues and fluids resulted in excellent clinical efficacy in a variety of infections ([6](#)). However, ciprofloxacin demonstrated limited activity against *Streptococcus pneumoniae*, and anaerobes at clinically achievable serum and tissue concentrations.

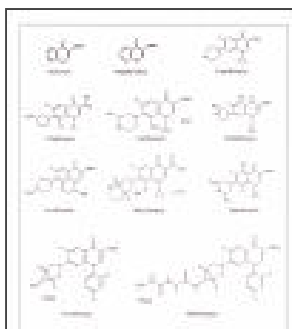
To improve the pharmacokinetic profile and antibacterial spectrum of ciprofloxacin, numerous modifications have been made to the fluoroquinolone structure. This paper reviews several of the antibiotics that have resulted from these modifications, namely clinafloxacin, gatifloxacin, grepafloxacin (Raxar, Glaxo Wellcome), levofloxacin (Levaquin, Janssen-Ortho), moxifloxacin, sparfloxacin and trovafloxacin (Trovan, Pfizer Canada Inc). Most and possibly all of these agents will soon become available in Canada. For the purposes of this review, the term 'new fluoroquinolones' will refer only to these seven agents. This review describes in detail the chemistry, mechanism of action, mechanisms of resistance, in vitro activity, pharmacokinetics, in vivo activity, adverse effects, drug interactions and pharmacoeconomic formulary considerations of the new fluoroquinolones. The objectives of this review are to summarize the information that is available on the new fluoroquinolones, to compare the various agents where possible and to point out the differences between the new fluoroquinolones and older agents in this class of antibiotics. Ciprofloxacin is included in parts of this review as a point of reference against which the new fluoroquinolones can be judged. However, for the most part, a discussion of this antibiotic is not provided in the text.

## CHEMISTRY

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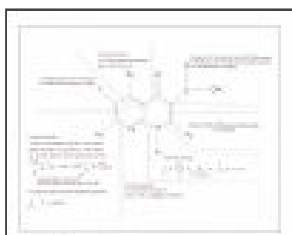
The majority of the new fluoroquinolones are analogs of the basic quinolone molecular structure ([Figure 1](#)). However, trovafloxacin

is based on a naphthyridine structure ([Figure 1](#)) (7). Important structural modifications have occurred at positions 1, 5, 7 and 8 ([Figure 1](#)), leading to the differences between the various agents. A summary of the structure activity relationships that have been documented for the fluoroquinolones is presented in [Figure 2](#) (8). The structures of the individual fluoroquinolone molecules and the intravenous prodrug of trovafloxacin (alatrofloxacin) are presented in [Figure 1](#) (9–15).



[Figure 1](#)

Chemical structures of quinolone, naphthyridine and fluoroquinolones



[Figure 2](#)

Structure activity relationships of the fluoroquinolones

Substituents at position 1 of the basic quinolone structure influence the potency of antibacterial activity. A cyclopropyl substituent at this position, as is found on all of the new fluoroquinolones except levofloxacin and trovafloxacin, is considered optimal for activity (7,8). The structure of levofloxacin ([Figure 1](#)) contains a third ring that links the N-1 and C-8 positions, resulting in increased activity of levofloxacin against Gram-positive bacteria, and a slight decrease in activity against *Pseudomonas aeruginosa* (7). Trovafloxacin ([Figure 1](#)) possesses a 2,4-difluorophenyl substituent at the N-1 position. This moiety increases potency, although not as much as a cyclopropyl group (8). The C-2 position of the basic quinolone structure is close to the DNA/DNA-gyrase binding site of the

fluoroquinolones, and, thus, a hydrogen at this position is optimal (8).

All of the new fluoroquinolones possess a carboxylic acid substituent at position 3 and a carbonyl group at position 4 ([Figure 1](#)). These groups are important for binding to the DNA/DNA-gyrase complex and for transport into bacterial cells (8,16). Chelate formation between these two groups and polyvalent metal ions (eg, aluminium<sup>+3</sup>, magnesium<sup>+2</sup>) results in drug interactions between the fluoroquinolones as a class and metal ion-containing drugs (eg, antacids, sucralfate) (8,17–19).

Position 5 of the quinolone ring is important in determining in vitro potency, especially against Gram-positive bacteria, and an amino substituent (as is found on sparfloxacin) is optimal here ([Figure 1](#)) (8). Grepafloxacin contains a methyl group at C-5 that increases in vitro potency against Gram-positive organisms to a lesser extent (8). The rest of the new fluoroquinolones lack a substituent at this position. A C-6 fluoro substituent, present in all of the new fluoroquinolones, enhances antibacterial potency and is the reason for the ‘fluoro’ nomenclature ([Figure 1](#)) (8).

Substituents at position 7 influence antibacterial potency, pharmacokinetics and the fluoroquinolone/theophylline interaction ([Figure 1](#)) (8). A piperazine ring at this position (eg, ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin and sparfloxacin) increases the potency of the fluoroquinolone against Gram-negative bacteria, while a pyrrolidine ring at this position (eg, clinafloxacin, moxifloxacin, trovafloxacin) improves the activity of the fluoroquinolone against Gram-positive bacteria (8). Alkyl substitution of either ring type (eg, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin, trovafloxacin) improves solubility (causing less risk of crystalluria), increases the activity of the fluoroquinolone against Gram-positive bacteria and prolongs the half-life of the fluoroquinolone (8). Nonbulky side chains at C-7, for example

piperazine and pyrrolidine side chains without alkyl groups and nonring-side chains, have been observed to result in fluoroquinolones that interact with theophylline (8). Hence, ciprofloxacin and clinafloxacin could both theoretically be expected to interact with theophylline (8). A theophylline interaction has also been reported for grepafloxacin (12).

Position 8 plays a role in determining both activity and adverse effects. Sparfloxacin and clinafloxacin are substituted with a halogen at this position. A halogen at position 8 expands the spectrum of antibacterial activity, yielding improved activity against anaerobes. However, phototoxicity, which is a class effect of the fluoroquinolones, is greatest with a halogen at C-8 (8). A methoxy substituent at position 8, which is part of the chemical structure of both gatifloxacin and moxifloxacin (Figure 1), similarly improves activity against anaerobes. This substituent causes a low incidence of phototoxicity (8). Mizuki et al (17) have published data that demonstrated that the substituent at C-8 is important in determining whether the fluoroquinolone/theophylline interaction occurs. A nitrogen at position 8, as is seen with trovafloxacin (Figure 1), predisposes a fluoroquinolone to such an interaction, while a halogen at this position is thought to be beneficial in preventing the interaction (8,17).

## MECHANISM OF ACTION AND MECHANISMS OF RESISTANCE

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### Mechanism of action:

Fluoroquinolones must accumulate intracellularly to kill bacterial cells. In Gram-negative bacteria, this is accomplished by passive diffusion, with the porin outer membrane proteins playing a role. Fluoroquinolone uptake into Gram-positive bacteria, such as *Bacillus subtilis*, appears to involve passive diffusion (20). Once inside bacterial cells, the fluoroquinolones have two targets.

The first of these targets is DNA gyrase, a type II topoisomerase composed of two A subunits (*gyrA*) and two B subunits (*gyrB*) (20,21). DNA gyrase introduces negative superhelical twists into bacterial DNA and, thus, is an essential enzyme in DNA replication (20,22). By inhibiting this enzyme, fluoroquinolones inhibit DNA synthesis (22). The exact binding site of fluoroquinolones within DNA gyrase is not precisely known. One proposed site is the DNA binding groove between the A and B subunits. Binding of the fluoroquinolones to this groove may conformationally change the DNA gyrase molecule. DNA itself may then become another binding site, thus resulting in the fluoroquinolones binding to both DNA and DNA gyrase (21). DNA gyrase is considered to be the primary site of fluoroquinolone action in many bacteria, including *E coli* (23).

The second target for the fluoroquinolones is topoisomerase IV, a heterotetramer made up of two ParC subunits (*parC*) and two ParE subunits (*parE*) (21,24). The protein subunits coded for by *parC* (ParC) and *parE* (ParE) are homologous to the A and B subunits of DNA gyrase, respectively (25). Topoisomerase IV carries out decatenation and relaxation of DNA, and assists with the segregation of replicating chromosomes or plasmids in bacteria (23–25). Inhibition of topoisomerase IV disrupts this process, contributing to the bactericidal activity of the fluoroquinolones. Results from studies on the development of high level resistance to fluoroquinolones in *S pneumoniae* and *Staphylococcus aureus* have demonstrated that for ciprofloxacin-selected mutants, the first step involves a mutation in *parC* (26,27). This suggests that topoisomerase IV is the primary target in these bacteria (26–28).

The primary target of fluoroquinolone action may be bacteria dependent (23,26–28). Topoisomerase IV and DNA gyrase can both also act as secondary targets. Hoshino et al (23) compared data collected on the inhibition of topoisomerase IV decatenation in *E coli* with data from other studies on the inhibition of DNA



gyrase supercoiling. They found that while the fluoroquinolones were more active in *E coli* against DNA gyrase, topoisomerase IV could act as a secondary target (23). Similarly, Gootz et al (26) found that high level resistance in *S pneumoniae* required a mutation in *gyrA* following the first mutation in *parC*. Some of the new fluoroquinolones (clinafloxacin, sparfloxacin and trovafloxacin) remain active against *S pneumoniae* that have a *parC* mutation, implying that either these compounds have a greater intrinsic potency against *S pneumoniae* or that different fluoroquinolones selectively target one enzyme over the other (26,29).

In summary, many details on the specific interactions of the various fluoroquinolones with DNA gyrase and topoisomerase IV have yet to be worked out. The primary target may depend on the type of bacteria and the specific fluoroquinolone. However, both DNA gyrase and topoisomerase IV are important targets.

### **Mechanisms of resistance:**

There are two main mechanisms of resistance to the fluoroquinolones, mutations involving the target sites (ie, DNA gyrase and topoisomerase IV) and mutations altering the accumulation of fluoroquinolones in bacteria. Considering target site alterations, high level resistance in ciprofloxacin-selected *S pneumoniae* mutants results from two mutations. The first occurs in *parC* and the second occurs in *gyrA* (26,28,29).

In sparfloxacin-selected *S pneumoniae* mutants, the first mutation arises in *gyrA* followed by a mutation in *parC* (29). The order in which the two mutations occur appears to be dependent, at least in *S pneumoniae*, on the fluoroquinolone used. In ciprofloxacin-selected *S aureus* mutants, the first mutation identified was in *parC*. This was followed by either a mutation in *gyrA* or a mutation resulting in reduced accumulation of the fluoroquinolones (27). In contrast, a *gyrA* mutation (altering DNA gyrase) is necessary for moderate resistance in *E coli*. Once this

mutation has occurred, a mutation in *parC* (altering topoisomerase IV) followed by a second *gyrA* mutation is required for the development of high level resistance (30). Mutations in the *gyrB* gene may also play a role in the development of resistance in *E coli* (31,32). Clinically, *gyrA* mutations in the quinolone resistance-determining region of the gene appear to be the most important cause of resistance in *E coli* (32).

Bacteria can also become resistant to the fluoroquinolones through reduced accumulation. One way this can happen in *E coli* is through mutations resulting in decreased expression of the porin outer membrane protein (OmpF), a route fluoroquinolones can enter into *E coli* (20,32,33). The second way that reduced accumulation of the fluoroquinolones can occur is through an efflux system. In *S aureus*, efflux of fluoroquinolones is mediated by the NorA protein which is coded for by *norA* (27,34–36). Resistance is due to increased expression (likely through a mutation in the regulatory region) of this chromosomal gene leading to increased efflux of the fluoroquinolones (36). This resistance mechanism is less important for hydrophobic quinolones such as sparfloxacin (27,34). This efflux system is not specific for fluoroquinolones, rather it is a multidrug exporter, whose likely normal physiological function is export of toxic substances (36). The existence of an efflux system in *P aeruginosa* has also been reported (37).

The different mechanisms of resistance do not affect all of the fluoroquinolones equally (26,29). In a study by Deguchi et al (38), gatifloxacin was found to possess minimum inhibitory concentrations (MICs) ranging from 0.06 to 1.0 µg/mL against fluoroquinolone-resistant isolates of *Neisseria gonorrhoeae* having mutations in both *gyrA* and *parC*. Additionally, Barry et al (39) found that pneumococci resistant to penicillin, cefotaxime (Claforan, Hoechst Marion Roussel) erythromycin, clindamycin (Dalacin C, Pharmacia & Upjohn Inc),



trimethoprim/sulfamethoxazole, tetracycline and chloramphenicol were still susceptible to cinafloxacin, sparfloxacin and trovafloxacin, suggesting that new fluoroquinolones may offer therapeutic solutions in the treatment of multidrug-resistant bacteria. Advantages of the new fluoroquinolones may include treating bacteria that are resistant to some of the older fluoroquinolones such as ciprofloxacin.

For *S pneumoniae*, the primary target is fluoroquinolone dependent. The primary target for ciprofloxacin, levofloxacin, moxifloxacin and trovafloxacin is ParC ([40,41](#)). *ParC* mutants display low level resistance (two- to eightfold increases in MIC) and are cross-resistant to all of the aforementioned agents, but not to gatifloxacin, sparfloxacin and cinafloxacin. GyrA is the primary target for gatifloxacin and sparfloxacin in *S pneumoniae* ([40,41](#)). *GyrA* mutants display low level resistance (two- to eightfold increases in MIC) to gatifloxacin and sparfloxacin but not to ciprofloxacin, levofloxacin, moxifloxacin, trovafloxacin and cinafloxacin ([40,41](#)). It is unclear whether ParC or GyrA is the primary target for grepafloxacin because both *parC* and *gyrA* mutants result in four- to eightfold increases in MIC ([41](#)). Double mutants in *parC* and *gyrA* result in high level resistance (16- to 64-fold increases in MIC) to ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin and trovafloxacin ([40,41](#)). Double mutants in *parC* and *gyrA* remain susceptible to cinafloxacin ([41](#)).

## IN VITRO ACTIVITY

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The in vitro activity of the new fluoroquinolones against clinically important bacterial species is summarized in [Tables 1–4](#) ([10,11,14,42–107](#)). These tables present the concentration of antibiotic necessary to inhibit 50% of isolates (MIC<sub>50</sub>) and 90% of isolates (MIC<sub>90</sub>). The MIC values represent the midpoint of the MIC<sub>50</sub> and MIC<sub>90</sub> values reported in the literature examined for each drug. Inclusion criteria for papers to be used in this portion

of the review were not restrictive as to growth conditions (including growth media) or the method used to carry out the study.

**TABLE 1**  
In vitro activity of the new fluoroquinolones and ciprofloxacin against Gram-positive aerobes

Bacteria	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Fluoroquinolone
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Staphylococcus aureus</i> (MR)	0.5	1	0.03	0.03	0.1	0.25	0.03
<i>S. aureus</i> (MR)	1	16	0.06	0.5	0.2	3.1	4
<i>Staphylococcus epidermidis</i> (MR)	0.25	1	0.06	0.12	0.1	3.1	0.06
<i>S. epidermidis</i> (MR)	1	16	0.25	1	0.1	3.1	0.12
<i>Staphylococcus saprophyticus</i>	0.5	0.5	0.06	0.12	NA	NA	0.12
<i>Staphylococcus pneumoniae</i>	0.5	1	0.06	0.06	0.25	0.5	0.25

**TABLE 1**

In vitro activity of the new fluoroquinolones and ciprofloxacin against Gram-positive aerobes

**TABLE 4**  
In vitro activity of the new fluoroquinolones and ciprofloxacin against other clinically important bacteria

Bacteria	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Fluoroquinolone
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Chlamydia pneumoniae</i>	1	2	NA	NA	0.062	0.12	NA
<i>Legionella pneumophila</i>	0.03	0.06	0.008	0.015	NA	NA	0.015
<i>Mycoplasma pneumoniae</i>	1	2	0.018	0.031	NA	0.06	NA
<i>Chlamydia trachomatis</i>	4	4	0.12	0.25	0.25	0.5	NA

**TABLE 4**

In vitro activity of the new fluoroquinolones and ciprofloxacin against other clinically important bacteria

All of the new fluoroquinolone antibiotics display improved activity against Gram-positive bacteria relative to ciprofloxacin ( [Table 1](#)) ([10,11,14,42–80](#)). Based only on MIC<sub>90</sub> values, the order of activity of the new fluoroquinolones against *S. aureus* (methicillin sensitive) is approximately clinafloxacin equal to trovafloxacin greater than grepafloxacin equal to moxifloxacin equal to sparfloxacin greater than gatifloxacin greater than levofloxacin greater than ciprofloxacin. Against *S. pneumoniae* (penicillin sensitive), the order of activity is clinafloxacin equal to moxifloxacin equal to trovafloxacin greater than grepafloxacin greater than gatifloxacin equal to sparfloxacin greater than levofloxacin greater than ciprofloxacin. A similar ranking is observed for penicillin-resistant *S. pneumoniae*. The order of activity by MIC<sub>90</sub> values versus *Enterococcus faecium* is clinafloxacin greater than trovafloxacin equal to sparfloxacin greater than ciprofloxacin equal to gatifloxacin equal to grepafloxacin equal to levofloxacin equal to moxifloxacin. None of the new fluoroquinolones has an MIC<sub>90</sub> value below 1.0 µg/mL against this pathogen, and the majority have an MIC<sub>90</sub> of greater than or equal to 4.0 µg/mL. Overall, clinafloxacin and

trovafloxacin are the most active of the new fluoroquinolones versus Gram-positive bacteria. Levofloxacin displays the least improvement relative to ciprofloxacin.

Similar to ciprofloxacin, the new fluoroquinolones demonstrate excellent activity against Gram-negative bacteria ([Table 2](#)) ([10,11,14,42,43–47,50,52,54,56–59,61,63,64,67–70,72–77, 80–84](#)). All of the new fluoroquinolones display MIC<sub>90</sub> values of less than 2 µg/mL against the majority of Gram-negative pathogens included in this review. Ranking the agents by MIC<sub>90</sub> values, the order of activity of the new fluoroquinolones against the enterobacteriaceae is approximately clinafloxacin greater than ciprofloxacin equal to levofloxacin equal to sparfloxacin greater than gatifloxacin equal to grepafloxacin equal to trovafloxacin greater than moxifloxacin. The ranking against *P. aeruginosa* is approximately clinafloxacin greater than ciprofloxacin greater than gatifloxacin equal to moxifloxacin equal to sparfloxacin equal to trovafloxacin greater than grepafloxacin greater than levofloxacin. Ciprofloxacin continues to display activity against Gram-negative bacteria that is either equivalent to or better than the activity demonstrated by the majority of the new fluoroquinolones (with the possible exception of clinafloxacin).

**TABLE 2**  
In vitro activity of the new fluoroquinolones against Gram-negative aerobes

Bacteria	Ciprofloxacin MIC <sub>50</sub> MIC <sub>90</sub>	Cinafloxacin MIC <sub>50</sub> MIC <sub>90</sub>	Gatifloxacin MIC <sub>50</sub> MIC <sub>90</sub>	Grepafloxacin MIC <sub>50</sub> MIC <sub>90</sub>	Trovafloxacin MIC <sub>50</sub> MIC <sub>90</sub>
<i>Acinetobacter baumannii</i>	0.25 1	0.03 0.25	0.06 0.5	0.025 0.025	
<i>Enterobacteriaceae</i>	0.03 0.12	0.03 0.12	0.2 0.78	0.06 0.06	
<i>Enterobacteriaceae</i>	0.015 0.25	0.016 0.5	0.05 0.1	0.03 0.03	
<i>Enterobacteriaceae</i>	0.015 0.25	0.008 0.016	0.05 0.1	0.03 0.03	
<i>Enterobacteriaceae</i>	0.015 0.12	0.015 0.03	0.05 0.1	0.008 0.008	
<i>Enterobacteriaceae</i>	0.004 0.004	0.004 0.008	0.013 0.025	0.004 0.004	
<i>Enterobacteriaceae</i>	0.004 0.008	NA NA	NA NA	NA 0.008	

**TABLE 2**

In vitro activity of the new fluoroquinolones against Gram-negative aerobes

The activity of the new fluoroquinolones against anaerobes is presented in [Table 3](#) ([10,14,45,47,52,54,56–59,68–70,75, 83,85,86–95](#)). The order of activity of the new fluoroquinolones against *Bacteroides fragilis* (again by MIC<sub>90</sub> values) is approximately clinafloxacin equal to trovafloxacin greater than moxifloxacin greater than gatifloxacin equal to sparfloxacin greater than levofloxacin greater than

ciprofloxacin equal to grepafloxacin. In a general sense, the anaerobic activity of new fluoroquinolones can be divided into three groups: those fluoroquinolones with greatly improved activity over ciprofloxacin (clinafloxacin, moxifloxacin, trovafloxacin); fluoroquinolones with moderately improved activity over ciprofloxacin (gatifloxacin, sparfloxacin); and fluoroquinolones with minimally improved activity over ciprofloxacin (grepafloxacin and levofloxacin).

TABLE 3  
In vitro activity of the new fluoroquinolones and ciprofloxacin against anaerobes

Bacteria	Ciprofloxacin MIC <sub>90</sub>	Ciprofloxacin MIC <sub>50</sub>	Clinafloxacin MIC <sub>90</sub>	Clinafloxacin MIC <sub>50</sub>	Gatifloxacin MIC <sub>90</sub>	Gatifloxacin MIC <sub>50</sub>	Grep. MIC <sub>90</sub>
Bacteroides fragilis	4	16	0.25	0.5	0.39	1.56	2
B. fragilis group	8	32	0.06	0.25	NA	NA	4
Clostridium difficile	8	16	0.5	2	0.78	1.56	8
Clostridium perfringens	0.25	1	0.06	0.13	0.39	0.39	0.5
Fusobacterium species	1	4	0.06	0.5	NA	0.39	1
Peptostreptococcus species	1	2	0.06	0.5	NA	3.13	1

TABLE 3

In vitro activity of the new fluoroquinolones and ciprofloxacin against anaerobes

Table 4 summarizes the activity of the new fluoroquinolones versus *Chlamydia pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Ureaplasma urealyticum* (68,94–105). The new fluoroquinolones all have MIC<sub>90</sub> values less than or equal to 1.0 µg/mL against *C pneumoniae*, 0.032 µg/mL against *L pneumophila*, 0.5 µg/mL against *M pneumoniae* and 1.0 µg/mL against *U urealyticum*.

PHARMACOKINETICS

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Table 5 shows the pharmacokinetic parameters of the new fluoroquinolone antibiotics following a single oral dose (3,6, 108–140). The kinetics of ciprofloxacin are well known, and this drug has been mostly excluded from the discussion that follows. The reader is referred to Wilson and Gruneberg (141) for a good review of the pharmacokinetics of ciprofloxacin. Each of the new fluoroquinolones is available as an oral formulation (109–111,125,142,143). Ciprofloxacin, clinafloxacin and levofloxacin are also available as intravenous formulations (142,143). Trovafloxacin can be administered intravenously as the prodrug alatrofloxacin (Figure 1). Alatrofloxacin, the L-alanyl- L-alanine

derivative of trovafloxacin, is rapidly converted to trovafloxacin in vivo, and is not detectable in the plasma approximately 5 mins after the infusion ([135](#)).

TABLE 5  
Pharmacokinetic parameters of the new fluoroquinolones and ciprofloxacin following

Drug	Dosage (mg)	F (%)	C <sub>max</sub> (mg/L)	T <sub>max</sub> (h)	AUC (mg·h/L)	T <sub>1/2</sub> (h)	VSF (L/kg)	Cl <sub>R</sub> (mL/min)
Ciprofloxacin	500	79	2.20	1.5	10.0	4.0	3.5	
	750	76	3.90	1.5	14.0	4.0	3.5	
Grepafloxacin	200	80	2.10	1.0	10.2	6.1	2.4	
Gatifloxacin	200	95	1.71	1.8	14.5	7.1	2.0	
	200	72	0.90	2.0	9.5	11.4	6.5	
Grepafloxacin	400	72	1.00	2.0	11.4	11.4	6.5	
	600	72	1.41	2.0	18.7	11.4	6.5	
Levofloxacin	500	99	5.30	1.4	40.0	6.7	1.2	
	750	99	7.10	1.4	62.0	6.7	1.2	
Moxifloxacin	200	86	1.20	1.8	15.3	11.0	3.0	
	400	86	1.55	1.8	16.0	11.0	3.0	

**TABLE 5**

Pharmacokinetic parameters of the new fluoroquinolones and ciprofloxacin following a single oral dose

## Absorption:

All of the new fluoroquinolones for which data exist have high oral bioavailability, ranging from 72% for grepafloxacin to 99% for levofloxacin ([Table 5](#)). For the most part, these agents are absorbed relatively quickly, reaching a peak concentration in the plasma approximately 1 to 2 h after oral administration ([Table 5](#)). Sparfloxacin is the exception. It is absorbed slowly in comparison with the other agents, and it reaches its peak concentration in the plasma approximately 4.5 h after being administered ([128–130](#)). The peak plasma fluoroquinolone concentration reached is variable, depending on the dosage administered. The effect of food on the pharmacokinetics of the new fluoroquinolones has been investigated for gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin and trovafloxacin ([120,127,137,144–146](#)). Food has been observed to slow the absorption of some of these agents (eg, levofloxacin, moxifloxacin, trovafloxacin) and to decrease the peak plasma concentration reached. However, in all cases the changes were not deemed by the investigators to be significant, and the extent of fluoroquinolone absorption (area under the plasma concentration time curve [AUC]) was unaffected. Hence, all of the six fluoroquinolones may be administered with or without food ([120,127,137,144–146](#)). Concomitant administration of intravenous morphine with oral trovafloxacin resulted in a 46% reduction in trovafloxacin peak

concentration reached in the plasma/serum ( $C_{max}$ ) and a 36% reduction in the AUC ([142](#)).

Distribution:

Similar to ciprofloxacin, the new fluoroquinolones have a high volume of distribution. This ranges from 1.2 L/kg for levofloxacin and trovafloxacin to 6.5 L/kg for grepafloxacin ([Table 5](#)). The new fluoroquinolones are extensively distributed into many tissues and fluids. The distribution of four of the new fluoroquinolones, grepafloxacin, levofloxacin, sparfloxacin and trovafloxacin, into selected tissues and fluids is presented in [Table 6](#) ([108,120,141,147–160](#)). Little data exist on the tissue and fluid distribution of the other agents. Grepafloxacin and sparfloxacin exhibit better penetration into respiratory tract tissues and fluids (eg, alveolar macrophages, bronchial mucosa and epithelial lining fluid), and inflammatory fluid than trovafloxacin, and better penetration into inflammatory fluid, gall bladder tissue and bile than levofloxacin ([Table 6](#)). This reflects the higher volume of distribution of these two agents relative to the other new fluoroquinolones ([Table 5](#)). The cerebrospinal fluid penetration of the new fluoroquinolones for which data were available (levofloxacin, sparfloxacin and trovafloxacin) is relatively low, with the fluid to serum ratio ranging from 0.16 for levofloxacin to 0.25 for sparfloxacin after administration of a single dose ([Table 6](#)). The fraction of each drug that is bound to plasma proteins is less than 80% ([Table 5](#)).

TABLE 6 Penetration of the new fluoroquinolones and ciprofloxacin into selected fluids and tissues				
Site	Tissue to serum or fluid to serum ratio (reference)			
	Ciprofloxacin (Sampling time 1 to 6 h postdose)	Grepafloxacin (Sampling time 2 to 5 h postdose)	Levofloxacin (Sampling time 1 to 6 h postdose)	Sparfloxacin (Sampling time 2 to 6 h post dose)
Alveolar macrophage	0.13 (130)	ND	0.23 (138)	0.22 (154)
Cerebrospinal fluid	0.37 (108)	ND	0.16 (138)	0.25 (154)
Gall bladder tissue	ND	6.22 (147)	1.42 (119,152)	7.1 (154) <sup>1</sup>
Bile	5.06 (139)	56.4 (147)	5.92 (119,152)	9.6 (154) <sup>1</sup>
Inflammatory fluid	1.17 (141)	1.83 (149)	0.96 (152)	1.37 (143)

**TABLE 6**  
Penetration of the new fluoroquinolones and ciprofloxacin into selected fluids and tissues

Elimination:



All of the new fluoroquinolones possess a longer half-life than ciprofloxacin, with the half-life of sparfloxacin (19 h) being the longest ([Table 5](#)). The elimination of clinafloxacin, gatifloxacin and levofloxacin is predominantly by renal excretion ([Table 5](#)). Grepafloxacin, moxifloxacin, sparfloxacin and trovafloxacin are eliminated mainly by nonrenal means ([Table 5](#)). Grepafloxacin requires a dosage adjustment in patients with mild hepatic impairment (Child-Pugh class A) and should not be used in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) ([117](#)). The dosage of levofloxacin must be adjusted in patients with renal impairment ([123,124](#)). Surprisingly, the dosage of sparfloxacin must be adjusted in patients with renal impairment, even though it is eliminated for the most part nonrenally. This may be the result of enterohepatic circulation of the sparfloxacin glucuronide, a metabolite of sparfloxacin. Hydrolysis of the glucuronide back to sparfloxacin may occur due to reduced excretion of this metabolite ([130](#)). Trovafloxacin does not appear to require a dosage adjustment in patients either with renal or hepatic impairment ([139,140](#)). No data exist on whether a dosage adjustment is necessary for clinafloxacin, gatifloxacin and moxifloxacin in patients with impaired renal or hepatic function.

## IN VIVO EFFICACY

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Clinical trials involving the new fluoroquinolones are summarized in [Tables 7.1](#) to [7.6](#) ([161–213](#)). The present review includes human clinical trials, without restrictions on design, sample size, etc. These trials were obtained by searching MEDLINE for English language trials published between the years 1995 and the first quarter of 1998, and reviewing relevant citations from all published articles. Abstracts more than two years old without subsequent publication of the data were excluded. The review primarily focuses on respiratory tract infections including chronic bronchitis and pneumonia, genitourinary tract infections, and skin and skin structure infections.

**TABLE 7.1**  
Results of clinical trials involving clinafloxacin

Author (reference)	Design	n	Indication	Regimen	Duration	R
<b>Respiratory tract infections</b>						
Lode (161)	Prospective, randomized, double-blind, open	156 (130)	Nosocomial pneumonia	C: 200 mg every 12 h (route not specified) Cefaz: 2 g intravenous every 8 h	NA NA 10 d 10 d 10 d 10 d 10 d 10 d 10 d 10 d	C: 1 (67) Cef: 1 (58)
<b>Intra-abdominal infections</b>						
Wilson	NA	101	NA	C: 200 mg	NA	C: 1

**TABLE 7.1**

Results of clinical trials involving clinafloxacin

**TABLE 7.6**  
Results of clinical trials involving trovafloxacin

Author (reference)	Design	n	Indication	Regimen	I
<b>Respiratory tract infections</b>					
Niederman et al (165) (166)	Prospective, randomized, double-blind	433 (362)	Community-acquired pneumonia	A: 200 mg iv every day followed by T 200 mg oral every day Cef: 3 g iv every day followed by cefixime 200 mg oral bid	1

**TABLE 7.6**

Results of clinical trials involving trovafloxacin

The in vivo efficacy of ciprofloxacin has been well documented elsewhere (6) and is not included in this section. No clinical trials involving moxifloxacin were identified, either in abstract form or published articles. Studies comparing the clinical efficacies of the new fluoroquinolones were not available; however, there are comparisons between several of the new fluoroquinolones and ciprofloxacin.

### Respiratory tract infections – *Clinafloxacin*:

Clinafloxacin (Table 7.1) has not been extensively evaluated in patients with respiratory tract infections. Preliminary data were obtained in an open, randomized study in which clinafloxacin was compared with ceftazidime in the treatment of nosocomial pneumonia (161). Clinafloxacin produced a cure (not defined) in 67% (46 of 69) of clinically evaluable patients and in 58% (25 of 43) of microbiologically evaluable patients. Ceftazidime produced cures in 64% (43 of 67) and 56% (24 of 43) of patients, respectively (161).

**Gatifloxacin:** Data are not available on the use of gatifloxacin to treat respiratory tract infections.

**Grepafloxacin:** Grepafloxacin has been studied in the treatment of acute bacterial exacerbations of chronic bronchitis in three trials (161–163). Chodosh et al (162) reported grepafloxacin to be equivalent to ciprofloxacin, both clinically and microbiologically. In this study, the most commonly isolated pathogens

were *Moraxella catarrhalis*, *S aureus*, *Haemophilus influenzae*, *S pneumoniae* and *Haemophilus parainfluenzae*. These pathogens were similarly distributed among the treatment groups. Grepafloxacin produced bacteriological eradication rates, defined as eradication or presumed eradication of the original pathogen, of 96% (400 mg every day) and 98% (600 mg every day) versus 92% for ciprofloxacin (500 mg bid) ([162](#)). The *S pneumoniae* eradication rates produced by both grepafloxacin regimens (75% for the 400 mg regimen and 88% for the 600 mg regimen) were superior to the eradication rate reported for ciprofloxacin (40%). However, the number of *S pneumoniae* isolates detected in this study was very small (21 altogether), leading the authors to conclude that these results were not clinically meaningful ([162](#)). A second study, conducted by Langan et al ([163](#)), demonstrated the equivalence of grepafloxacin and amoxicillin in producing a successful clinical outcome. *H influenzae*, *S pneumoniae* and *M catarrhalis* were the pathogens most frequently isolated, and these were similarly distributed among the treatment groups. At the end of treatment, grepafloxacin at daily doses of 400 mg and 600 mg yielded microbiological success rates (defined as eradication or presumed eradication of the original pathogen) of 97.1% and 98.2%, respectively, versus 88.8% for amoxicillin. Grepafloxacin produced eradication rates against *H influenzae* (99% for the 400 mg regimen and 100% for the 600 mg regimen) that were superior to the eradication rate produced by amoxicillin (89%) ([163](#)). In an abstract published by Kobayashi et al ([164](#)), grepafloxacin was demonstrated to be clinically equivalent to ofloxacin. The predominant pathogens isolated in this trial were *S aureus*, *S pneumoniae*, *H influenzae* and *P aeruginosa*. Grepafloxacin produced a bacteriological eradication rate of 72.9% compared with 84.2% for ofloxacin. The authors reported that there was “no significant difference” between the two groups in terms of bacterial eradication ([164](#)).

Two prospective, randomized, double-blind, comparative studies have been published investigating the efficacy of grepafloxacin in the treatment of community-acquired pneumonia ([165,166](#)). These studies found that grepafloxacin was similar to amoxicillin and clarithromycin in producing a clinical cure. In one study, grepafloxacin was found to be microbiologically superior to amoxicillin. In the grepafloxacin group, 88.2% of *H influenzae* (15 of 17) and *S pneumoniae* (15 of 17) isolates were eradicated or presumed eradicated at follow-up (28 to 42 days post-treatment) as opposed to only 66.7% of *H influenzae* (16 of 24) and *S pneumoniae* (eight of 12) isolates in the amoxicillin group. The *S pneumoniae* isolates in this study included four strains that were intermediately resistant and four strains that were fully resistant to penicillin ([165](#)). The other study by Patel et al ([166](#)), published as an abstract, reported statistically equivalent bacteriological cures achieved for grepafloxacin (92%) and clarithromycin (91%). The predominant pathogens isolated in this study were *S pneumoniae*, *H influenzae*, *S aureus*, *M catarrhalis* and *H parainfluenzae* ([165](#)). A third study, published in abstract form, investigated grepafloxacin in the treatment of pneumonia ([167](#)). Grepafloxacin was not statistically different from ofloxacin in terms of clinical efficacy or bacterial eradication ([167](#)). The bacteriological eradication rates were 96.4% in the grepafloxacin group and 97% in the ofloxacin group. *S aureus*, *S pneumoniae* and *H influenzae* were the main causative bacteria in this study ([167](#)).

**Levofloxacin:** Three trials examining the efficacy of levofloxacin in the treatment of acute exacerbations of chronic bronchitis have been carried out ([Table 7.4](#)) ([168–170](#)). These trials have shown levofloxacin to be both equivalent to cefuroxime axetil and cefaclor, in terms of clinical and microbiological efficacy ([166–168](#)). DeAbate et al ([168](#)) reported a bacteriological eradication rate of 97.4% for levofloxacin versus 94.6% for cefuroxime axetil (Ceftin, Glaxo Wellcome). In another study, levofloxacin and

cefaclor (Ceclor, Lilly) produced bacteriological eradication rates of 94% and 87%, respectively (170). The most common pathogens isolated in these trials were Gram-negative aerobes and *S pneumoniae* (168–170).

TABLE 7.4 Results of clinical trials involving levofloxacin					
Author (reference)	Design	n (Q)	Indication	Regimen	Out
Respiratory tract infections					
Chikatsu et al (171)	Prospective, randomized, open	452 (452)	Acute exacerbation of chronic bronchitis	L 500 mg oral every day	Mo 7 L
				Cef ax 250 mg oral bid	Mo 10

TABLE 7.4  
Results of clinical trials involving levofloxacin

Two prospective, randomized, double-blind trials have been conducted that specifically investigated levofloxacin as a treatment for community-acquired pneumonia (171,172). Levofloxacin demonstrated a clinical success rate of 96% in a trial by File et al (171) and 95% (when taken once daily) or 94% (when taken twice daily) in a trial by Carbon et al (172). Additionally, it was found to be clinically equivalent to amoxicillin/clavulanic acid, and superior to a regimen of ceftriaxone (Rocephin, Roche) and/or cefuroxime axetil (Table 7.4). *S pneumoniae*, *H influenzae*, *S aureus* and the atypical bacteria (*C pneumoniae*, *M pneumoniae*, *L pneumophila*) were the primary pathogens identified in the two studies (171,172). The eradication rate (against typical pathogens) of levofloxacin (98%) was found to be superior to the eradication rate produced by the regimen of ceftriaxone and/or cefuroxime axetil (85%) (171). Carbon et al (172) demonstrated an equivalent eradication rate for levofloxacin (97.8% for daily dosing or 100% for twice daily dosing) and amoxicillin/clavulanic acid (97.5%).

Levofloxacin has also been studied in a number of noncomparative trials (published as extended abstracts) in the treatment of other respiratory tract infections, such as bronchiectasis, bronchitis and bronchopneumonia. These trials involved smaller numbers of subjects than the trials reported above. Overall, levofloxacin demonstrated ‘excellent’ or ‘good’ clinical efficacy (based on clinical signs and symptoms,

laboratory results and chest x-rays) in approximately 80% to 100% of the patients in these trials ([173–176](#)).

**Sparfloxacin:** Sparfloxacin ([Table 7.5](#)) has been extensively studied as a treatment for respiratory tract infections. Three prospective, randomized, double-blind trials have been performed where sparfloxacin was used to treat acute exacerbations of either chronic bronchitis or chronic obstructive pulmonary disease ([177–179](#)). The end of treatment clinical success for sparfloxacin was 85% in the study by DeAbate et al ([177](#)) and 87% in the study by Allegra et al ([178](#)). The follow-up success rate at 10 days post-treatment was 79% ([177](#)). Sparfloxacin was shown to be at least as effective as the two comparators, ofloxacin and amoxicillin/clavulanic acid, in producing a clinical cure and eradicating the causative pathogens ([177,178](#)). In the study by Allegra et al ([178](#)), the eradication rate for bacteriologically evaluable patients was 86.4% for sparfloxacin and 82.1% for amoxicillin/clavulanic acid. The bacteria most frequently isolated in these two studies included *S pneumoniae*, *H influenzae*, *M catarrhalis*, *C pneumoniae*, *H parainfluenzae*, *P aeruginosa* and the *Enterobacteriaceae* ([177,178](#)). In a study by Taytard et al ([177](#)), the overall efficacy of sparfloxacin (86%) was equivalent to the overall efficacy of amoxicillin/clavulanic acid (85%). This study did not provide a microbiological analysis ([179](#)).

TABLE 7.5 Results of clinical trials involving sparfloxacin					
Author (reference)	Design	n (%)	Indication	Regimen	Duration
DeAbate et al (177)	Prospective, randomized, double-blind	788 (55%)	Acute bacterial exacerbations of chronic bronchitis	5-400 mg oral qid	10-14
Allegra et al (178)	Prospective, randomized, double-blind	200	Acute bacterial exacerbations of chronic bronchitis	5-400 mg oral qid	10-14
Taytard et al (179)	Prospective, randomized, double-blind	200	Acute bacterial exacerbations of chronic bronchitis	5-400 mg oral qid	10-14

**TABLE 7.5**  
Results of clinical trials involving sparfloxacin

Six studies, two of which were available as abstracts, have been conducted to examine the efficacy of sparfloxacin in community-acquired pneumonia ([180–185](#)). Clinically, sparfloxacin has demonstrated comparable efficacy to amoxicillin, amoxicillin/clavulanic acid, erythromycin, cefaclor and amoxicillin with ofloxacin, and superior efficacy with



roxithromycin. The success rate for sparflloxacin in these trials ranged from 84% to 95%, depending in part on how long after treatment the patients were evaluated. Additionally, sparflloxacin was found to display a superior bacteriological response over erythromycin (91.7% versus 75.9%) ([181](#)) and cefaclor (91.9% versus 83.8%) ([182](#)), and at least an equivalent bacteriological response to the other comparators. The predominant pathogens isolated included *S pneumoniae*, *H influenzae*, *M pneumoniae*, *C pneumoniae* and *H parainfluenzae* ([180–185](#)).

**Trovafloxacin:** Trovafloxacin ([Table 7.6](#)) has been studied as a treatment for pneumonia in several trials. Two prospective, randomized, double-blind trials have been published examining the efficacy of trovafloxacin in the treatment of community-acquired pneumonia ([186,187](#)). In these trials, trovafloxacin alone or trovafloxacin and alatrofloxacin were found to be statistically equivalent to the comparators ceftriaxone/cefpodoxime with or without erythromycin and clarithromycin in terms of producing a successful clinical outcome ([Table 7.6](#)) ([186,187](#)). In the trial conducted by Niederman et al ([186](#)), the isolated pathogens included *S pneumoniae*, *H influenzae*, *S aureus*, *M catarrhalis*, *L pneumophila*, *M pneumoniae* and *C pneumoniae*. Alatrofloxacin, followed by trovafloxacin, was shown to be as effective in the microbiologically evaluable patients as the alternative regimen of ceftriaxone/cefpodoxime with or without erythromycin ([186](#)). A summary of six trials in which trovafloxacin (or alatrofloxacin) was used to treat community-acquired pneumonia caused by *S pneumoniae* revealed that the clinical efficacy of trovafloxacin/alatrofloxacin was 93% at the end of treatment and 91% at follow-up. The combined results for the comparators in the six trials were 94% and 88%, respectively (comparators are listed in [Table 7.6](#)). A statistical analysis of these results was not provided ([188](#)). When trovafloxacin/alatrofloxacin was investigated for the treatment of nosocomial pneumonia, the clinical success was 77% of those treated with

trovafloxacin/alatrofloxacin versus 78% of those treated with ciprofloxacin with or without clindamycin or metronidazole. The two regimens were reported to be statistically equivalent. A microbiological analysis was not provided (189).

**Genitourinary tract infections – Clinafloxacin:**

Data are not available on the use of clinafloxacin to treat genitourinary tract infections.

**Gatifloxacin:** One open noncomparative trial was identified examining the efficacy of gatifloxacin in the treatment of genitourinary tract infections (Table 7.2). Suzuki et al (190) investigated the use of gatifloxacin to treat chronic bacterial prostatitis and reported its overall efficacy to be 91%. Additionally, bacterial eradication was achieved against 100% of the strains isolated. Bacteria were cultured from expressed prostatic secretions. The bacteria isolated in this trial included *E coli*, *Enterococcus faecalis*, *Staphylococcus epidermidis* and *Streptococcus agalactiae*. Three of nine patients available for follow-up relapsed within two to four weeks. This led the investigators to suggest that a longer course of therapy, beyond the 14 days used in this study, may be required (190).

TABLE 7.2  
Results of clinical trials involving gatifloxacin

Author (reference)	Design	n (n)	Indication	Regimen	Duration
Gonorrhoea and chlamydia					
Suzuki K et al (190)	Noncomparative, open	33	Chronic bacterial prostatitis	Gatifloxacin 200 mg oral bid	14 days

**TABLE 7.2**  
Results of clinical trials involving gatifloxacin

**Grepafloxacin:** Three trials have been conducted in which grepafloxacin has been used to treat genitourinary tract infections (Table 7.3) (191–193). The first of these compared grepafloxacin with cefixime in the treatment of uncomplicated gonorrhea in men. This study found that both drugs produced high cure rates (99% for grepafloxacin and 97% for cefixime) as defined by eradication of the causative pathogen, *N gonorrhoeae* (191). Another study, published in abstract form, examined the efficacy

of grepafloxacin relative to ofloxacin in 244 patients with gynecological infections. It was found that the two drugs were similar in terms of clinical and bacteriological efficacy ([Table 7.3](#)) ([192](#)). The third study was a dose ranging study investigating the treatment of *Chlamydia trachomatis* infections in women who were using grepafloxacin. This study found grepafloxacin to be effective, as determined by a reduction in signs and symptoms of infection and negative culture results at the follow-up visit ([193](#)). In addition, Mroczkowski et al ([194](#)), published as an abstract, demonstrated comparable clinical success for a single dose of grepafloxacin 400 mg and cefixime 400 mg in the treatment of gonococcal cervicitis in women.

TABLE 7.3 Results of clinical trials involving grepafloxacin					
Author (reference)	Design	n (%)	Indication	Regimen	CR
Respiratory tract infections					
Choudhri et al (192)	Prospective, randomized, double-blind	624 (467)	Acute bacterial exacerbations of chronic bronchitis	G: 400 mg oral every day (n=312)	3

**TABLE 7.3**  
Results of clinical trials involving grepafloxacin

**Levofloxacin:** The efficacy of levofloxacin in the treatment of genitourinary tract infections has been the subject of a small number of trials ([Table 7.4](#)). The results from two studies in which levofloxacin was used to treat acute pyelonephritis were combined and analyzed. Levofloxacin produced a clinical success rate of 93% versus 95% for ciprofloxacin and lomefloxacin, which were used as comparators. Against the pathogens most commonly isolated in the two trials, *E coli*, *Klebsiella pneumoniae* and *Staphylococcus saprophyticus*, levofloxacin was found to be at least as effective as ciprofloxacin and lomefloxacin ([195](#)). The use of levofloxacin to treat complicated urinary tract infections was investigated by Klimberg et al ([196](#)). Levofloxacin produced a clinical success (defined as cure or improvement) in 93% of patients versus 88% for lomefloxacin, which was used as a comparator. The eradication rate produced by levofloxacin (98.9%) against *E coli*, the pathogen most frequently isolated in this study, was not significantly different from the eradication rate produced by lomefloxacin (97.6%) against this pathogen ([196](#)).

Levofloxacin has also been investigated in the treatment of nonchlamydial chronic prostatitis. Levofloxacin produced a clinical success rate of 75%. This trial was noncomparative and involved a relatively small number of participants ([197](#)).

**Sparfloxacin:** Seven studies have been carried out examining the efficacy of sparfloxacin in the treatment of genitourinary tract infections ([Table 7.5](#)) ([198–204](#)). Sparfloxacin has been compared with ciprofloxacin in the treatment of acute gonococcal urethritis in men. Efficacy, defined in part by the eradication of *N gonorrhoeae*, was achieved in 99% of patients treated with sparfloxacin and in 98% of patients treated with ciprofloxacin ([198](#)). Phillips et al ([199](#)) investigated two regimens of sparfloxacin as a treatment for nongonococcal urethritis in men. Overall, both regimens were found to be statistically equivalent to doxycycline, which was used as the comparator. *C trachomatis* and *U urealyticum* were the pathogens isolated in this study. The eradication of *C trachomatis*, specifically, was not as high at follow-up in the three-day sparfloxacin group (88.1%) as it was in the seven-day sparfloxacin group (97%) or doxycycline group (96.1%) ([199](#)).

Three trials have focused on the treatment of urinary tract infections with sparfloxacin ([200–202](#)). Naber et al ([200](#)) studied sparfloxacin in the treatment of complicated urinary tract infections. The overall efficacy of sparfloxacin (71%) was found to be lower than the overall efficacy of ciprofloxacin (77%). Sparfloxacin was significantly less effective than ciprofloxacin in producing a bacteriological cure. These results were attributed to a lower activity of sparfloxacin against *Enterobacteriaceae* (other than *E coli*), *P aeruginosa* and enterococci ([200](#)). Sparfloxacin has been used to treat community-acquired, acute, uncomplicated urinary tract infections in two studies, published as abstracts. Both one-day and three-day regimens of sparfloxacin produced a successful clinical response in about 93% of patients.

Sparfloxacin was found to be equivalent to ciprofloxacin and ofloxacin in producing a clinical response ([201,202](#)).

An open label, noncomparative trial investigated the efficacy of sparfloxacin in treating uncomplicated urinary tract infections, complicated urinary tract infections, urethritis and prostatitis. Clinical efficacy was 100%, 65%, 93% and 79%, respectively, in patients treated for these infections. Several dosage regimens were used in this trial. Clinical efficacy in the patients that received 300 mg once daily was found to be higher than that in patients who received 200 mg once daily ([203](#)).

The efficacy of sparfloxacin in treating gynecological infections has been the subject of a single, noncomparative trial available as an extended abstract ([204](#)). Sparfloxacin produced a clinical response that was either 'excellent' or 'good' in 97% of patients with adnexitis, 94% of patients with endometritis, 98% of patients with cervicitis and 100% of patients with other gynecological infections. The pathogens isolated in this study included Gram-positive bacteria, Gram-negative bacteria and anaerobes. Overall, 91.3% of the bacterial strains isolated were eradicated by treatment with sparfloxacin ([204](#)).

**Trovafloxacin:** The efficacy of trovafloxacin in the treatment of genitourinary tract infections has been evaluated in two trials ([Table 7.6](#)) ([205,206](#)). The first of these was a noncomparative dose ranging study that examined the use of trovafloxacin in the treatment of uncomplicated gonorrhea. It was found that all three dosage regimens produced a cure in 100% of patients treated, as determined by post-treatment culture results ([205](#)). Jones et al ([206](#)) conducted another trial involving a larger number of patients. In this prospective, randomized, double-blind trial, trovafloxacin was used to treat patients with uncomplicated gonococcal urethritis or cervicitis. Eradication rates and clinical responses in the trovafloxacin group were equivalent to those in the ofloxacin group. Ninety-six per cent of patients treated with

trovafloxacin showed a clinical response of either cure or improvement ([206](#)).

### **Skin and skin structure infections – *Clinafloxacin*:**

Data are not available on the use of clinafloxacin to treat skin and skin structure infections.

**Gatifloxacin:** Data are not available on the use of gatifloxacin to treat skin and skin structure infections.

**Grepafloxacin:** The use of grepafloxacin in treating skin and skin structure infections has been investigated in one trial ([Table 7.3](#)) ([207](#)). Patients enrolled in this study had either deep-seated hair follicle infections (eg, furunculosis) or deep-seated diffuse infections (eg, cellulitis). Grepafloxacin was found to be 90% efficacious in treating these patients, and was equivalent to ofloxacin in the treatment of skin and skin structure infections. Criteria used to evaluate efficacy were not described in the abstract ([207](#)).

**Levofloxacin:** Two trials were identified that examined the use of levofloxacin for the treatment of skin and skin structure infections ([Table 7.4](#)). In a randomized trial performed by Nicodemo et al ([208](#)), levofloxacin was compared with ciprofloxacin in the treatment of uncomplicated infections, which included abscesses, impetigo, furuncles, cellulitis and pyoderma. The most common pathogens isolated were Gram-positive aerobes (*S aureus* and *Streptococcus pyogenes*). Levofloxacin and ciprofloxacin were found to be equivalent, both clinically and microbiologically. The clinical success rates of levofloxacin and ciprofloxacin were 96% and 94%, respectively ([208](#)). Nichols et al ([209](#)) conducted another trial comparing levofloxacin with ciprofloxacin in the treatment of skin and skin structure infections. In this study, cellulitis was the most common diagnosis in both treatment groups, occurring in approximately 47% of patients. Treatment with levofloxacin resulted in a clinical success



(cure or improvement) in 98% (178 of 182) of patients versus 94% (182 of 193) for ciprofloxacin ([209](#)).

**Sparfloxacin:** The efficacy of sparfloxacin in the treatment of skin and skin structure infections has been studied in three trials (all published as abstracts) ([210–212](#)) ([Table 7.5](#)). In the first of these, the clinical response rate of sparfloxacin was statistically equivalent to that of ciprofloxacin, with 90% of sparfloxacin-treated patients and 87% of ciprofloxacin-treated patients cured or improved. Sparfloxacin demonstrated a higher bacterial eradication rate than ciprofloxacin (87% versus 80%). A statistical analysis of this result was not provided. Gram-positive cocci were the most frequently isolated pathogens in this study ([210](#)). The remaining two studies were noncomparative. In both of these trials, treatment with sparfloxacin resulted in an ‘excellent’ or ‘good’ clinical response in 87% of patients ([211,212](#)). Overall, sparfloxacin displayed an eradication rate of 92.7% in the study conducted by Watanabe et al ([212](#)). The most common pathogens isolated in this study were coagulase-negative staphylococci, *S aureus* and *E coli* ([212](#)).

**Trovafoxacin:** Data are not available on the use of trovafoxacin to treat skin and skin structure infections.

### **Intra-abdominal infections – Clinafloxacin:**

Clinafloxacin has excellent activity against Gram-positive and Gram-negative aerobes and anaerobes (see section on In Vitro Activity), making it a potentially useful therapy in the treatment of intra-abdominal infections ([Table 7.1](#)). Wilson ([213](#)) conducted a study of intra-abdominal infections from a variety of causes, including appendicitis, bowel perforation and diverticulitis. Results demonstrated a cure rate of 76% in the evaluable population. Furthermore, clinafloxacin was found to be equally as efficacious as imipenem in the treatment of intra-abdominal infections ([213](#)).

## OVERALL EVALUATION

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Traditionally, the fluoroquinolones have been considered to have only moderate activity against streptococci. Consequently, older fluoroquinolones are not first-line agents in the treatment of lower respiratory tract infections. A recent review of ciprofloxacin presents convincing evidence that this drug may not be significantly different from comparators in the treatment of lower respiratory tract infections ([6](#)). However, because there is increased concern with the development of penicillin-resistant *S pneumoniae*, new fluoroquinolones with good activity against *S pneumoniae* are of interest. The new fluoroquinolones appear to perform well in vivo. They are considered as part of the therapeutic regimens for the treatment of community-acquired pneumonia as indicated in the recent management guidelines from the Infectious Diseases Society of America ([214](#)).

The new fluoroquinolones that have been studied in the treatment of genitourinary tract, and skin and skin structure infections have also yielded promising results. These agents were all found to be at least as efficacious as their comparators. However, it should be stated that fluoroquinolones are an evolving treatment for skin and soft tissue infections, while cloxacillin, clindamycin, cephalexin, etc, remain excellent first-line choices. Several of the new fluoroquinolones demonstrate improved activity against anaerobes (clinafloxacin, gatifloxacin, moxifloxacin, sparfloxacin and trovafloxacin). These agents may be suitable for the treatment of anaerobic, or mixed aerobic/anaerobic infections. Clinafloxacin has demonstrated favourable results in one study where it was used to treat intra-abdominal infections.

Overall, the clinical efficacy of the new fluoroquinolones is very promising. Based on the dosage regimens used in clinical trials, once daily dosing appears to be appropriate with a number of these agents. Adverse effects, drug interactions, pharmacokinetics and cost also play a major role in decision-making, and these are

discussed in other sections of this review. In addition, it is very important to consider the wide scale use of fluoroquinolones in the context of the potential for development of antimicrobial resistance. High level resistance to one fluoroquinolone ensures resistance to all others (except ciprofloxacin) (215). Although the new fluoroquinolones may seem ideal for multiple indications, it is important to reserve their use for specific indications where other conventionally used agents would not be suitable.

ADVERSE EFFECTS

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Gastrointestinal side effects, central nervous system disturbances and allergic manifestations are the most frequently encountered adverse effects of the new fluoroquinolones (Table 8) (6,143,144,161–163,165,167,171,189,213,216–224). Because a direct comparison between the various agents has not been performed in clinical trials, the data represent the approximate frequency of adverse effects with which side effects have been reported in the literature. The new fluoroquinolones for which data exist have all been observed to cause nausea, vomiting and diarrhea to some degree (Table 8).

TABLE 8 Frequently occurring adverse effects of the new fluoroquinolones and ciprofloxacin				
Adverse effect	Ciprofloxacin	Cinoxacin	Gatifloxacin	Grepafloxacin
Central nervous system				
Nausea	+	ND	+	++
Vomiting	+	ND	ND	+
Diarrhea	+	++	+	+
Central nervous system				
Dizziness	+	ND	+	+
Headache	+	ND	+	+
Allergic				
Rash	+	ND	ND	+
Pruritis	++	ND	ND	+

TABLE 8  
Frequently occurring adverse effects of the new fluoroquinolones and ciprofloxacin

Central nervous system side effects:

Central nervous system side effects, specifically dizziness and headache, have been reported for many of the new fluoroquinolones (Table 8). Trovafloxacin causes the highest incidence of dizziness (approximately 11%) (223). Levofloxacin and sparfloxacin have to date not been observed to produce this particular adverse effect. The incidence of headache resulting from treatment with the new fluoroquinolones is similar for all of

the agents for which data were available, with roughly 1% to 5% of patients treated reporting this side effect ([Table 8](#)).

### **Allergic reactions:**

Rash and pruritis have been reported relatively frequently for several of the new fluoroquinolones ([Table 8](#)). These adverse effects have not been observed for levofloxacin.

### **Cardiovascular side effects:**

Grepafloxacin and sparfloxacin have both been observed to cause prolongation of the QTc interval ([218,222](#)). Little data exist on the clinical relevance of this adverse effect for grepafloxacin.

Sparfloxacin causes a 3% increase in the QTc interval on average, and this is not increased in patients with impaired hepatic or renal function ([222](#)). These two fluoroquinolones should be used with extreme caution, if at all, in patients with underlying cardiac conditions, such as pre-existing QT prolongation, and in patients taking other medications known to prolong the QTc interval (see section on Drug Interactions) ([218,222,225](#)).

### **Phototoxicity:**

Phototoxicity, a class effect common to all of the fluoroquinolones, appears to result from an interaction between ultraviolet A (UVA) light and the fluoroquinolone molecule. This interaction produces photodegradation products and/or reactive oxygen species that may result in tissue damage ([5,226](#)).

Clinafloxacin and sparfloxacin cause a significantly higher incidence of phototoxicity than the other agents (1.5% to 14% and 2% to 11%, respectively) ([213,227](#)). The phototoxic potential of the new fluoroquinolones is approximately sparfloxacin equal to clinafloxacin much greater than grepafloxacin greater than levofloxacin equal to ciprofloxacin greater than trovafloxacin ([13,213,216,217,217,224,228](#)). Not enough data have been collected on gatifloxacin or moxifloxacin to include them in this

ranking. The phototoxicity of sparfloxacin is particularly severe, and in France and Japan, approximately 10% to 15% of phototoxicity cases involving sparfloxacin have been serious, requiring hospitalization ([227](#)). Measures to prevent this adverse effect include avoiding UVA sunlight, wearing protective clothing and using a broad spectrum sunscreen that blocks UVA light even on cloudy days and with window glass-transmitted sunlight ([5](#)).

### **Hepatotoxicity:**

Recently, 53 cases of hepatotoxicity have been reported with trovafloxacin (personal communication, Pfizer Inc). With over 1,200,000 patients who have received trovafloxacin, this yields a frequency of approximately one in 20,000 cases. Hepatotoxicity has ranged from asymptomatic elevations in hepatic enzymes to clinical jaundice. The majority of these patients had pre-existing hepatic abnormalities or were receiving concomitant potential hepatotoxins (personal communication, Pfizer Inc). The exact role that trovafloxacin has in causing or contributing to hepatotoxicity needs to be better delineated.

### **Paediatric concerns:**

The fluoroquinolones are contraindicated in children, in adolescents in the growing phase, and during pregnancy and lactation ([229](#)). The reason for these contraindications is that many of the older fluoroquinolones have been observed to induce cartilage toxicity when administered to immature animals. When the animals presented with clinical symptoms, the joint lesions presented as acute arthritis, with limping and swelling ([230](#)). Cartilage toxicity in animals appears to be caused by all of the fluoroquinolones to some degree. However, it appears that fluoroquinolones only very rarely cause arthropathy in humans ([230](#)). In a review that examined the adverse effects documented in more than 1500 children and adolescents who were administered ciprofloxacin, the safety profile of this drug was

found to be similar to the safety profile in adults (231). Gastrointestinal, dermatological and central nervous system side effects were the adverse events most commonly observed. Arthralgia was rarely documented and always reversible. In 1113 patients with cystic fibrosis, reversible arthralgia occurred in 36 (3.2%) (231). Thus, in the treatment of severe, life-threatening diseases, the benefit of fluoroquinolone use in children appears to outweigh the risk (229). However, because the potential to cause harm exists, further study is needed before the fluoroquinolones can be recommended for routine use in paediatric patients. A study by Martell et al (232) assessed whether growth of preterm infants was affected by administration of a fluoroquinolone. This study reported lower weight and smaller head circumference in the fluoroquinolone-treated individuals, relative to a reference group. It was not clear whether this was due to treatment with a fluoroquinolone or another variable such as the severity of illness (232).

DRUG INTERACTIONS

Go to:

A number of studies have been published examining potential interactions between the new fluoroquinolones and various other drugs. Table 9 presents some of the more common and/or potentially serious drug interactions of the new fluoroquinolones (6,9,13,129,218,222,231–251).

TABLE 9 Drug interactions of the new fluoroquinolones				
Interaction with	Ciprofloxacin	Clarithromycin	Gatifloxacin	Grepafloxacin
Metal ion-containing drugs (eg antacids, iron, zinc)	Yes	Yes	Yes	Yes
Mechanism	Chelation resulting in reduced fluoroquinolone bioavailability			
Recommendation	Avoid concurrent administration if possible. Otherwise, administer with food			
Theophylline	Yes (++)	Yes (++)	Yes (++)	Yes (++)
Mechanism	Inhibition of theophylline metabolism, resulting in increased theophylline levels			
Recommendation	For ciprofloxacin and clarithromycin, monitor theophylline level and adjust theophylline dose by 50% and monitor theophylline toxicity			
Warfarin	Yes/No	Yes	Yes	No

TABLE 9  
Drug interactions of the new fluoroquinolones

Metal ion-containing drugs:

Interactions have been observed (or are anticipated to occur) between metal ion-containing drugs and all members of the fluoroquinolone class of antibiotics (Table 9).



These interactions are thought to be predominantly the result of chelate (complex) formation between polyvalent metal cations and the fluoroquinolone molecules (8,17–19). The chelates formed are insoluble, and, thus, the bioavailability of the fluoroquinolones is decreased (18). Metal ion-containing drugs that interact with the new fluoroquinolones include aluminum- and magnesium-containing antacids, ferrous sulphate and sucralfate, which is a complex of aluminum hydroxide and sulphated sucrose (18). Metal ion-containing drugs have been reported to cause a reduction in fluoroquinolone bioavailability ranging from 19% to 88%, depending on the specific metal ion-containing drug and the specific fluoroquinolone (6,129,233–239). Iron has less of an impact than sucralphate and antacids (17,18,233). It is uncertain as to whether calcium affects the bioavailability of the new fluoroquinolones to any extent. To avoid therapeutic failure, concomitant administration of metal ion-containing drugs and fluoroquinolones should be avoided (6,18,235). If this is not feasible, the fluoroquinolone should be administered at least 2 h before or 6 h after the ingestion of the metal ion-containing drug (6,236,240).

### **Theophylline:**

The metabolic enzyme cytochrome P450 1A2 can be inhibited by several of the fluoroquinolones (ciprofloxacin, clinafloxacin, grepafloxacin), resulting in reduced clearance of theophylline (241,242). This can lead to increased serum theophylline levels and potential toxicity (6,241). A 600 mg daily dose of ciprofloxacin has been observed to cause an increase in the  $C_{\max}$  and AUC of theophylline of 17% and 22%, respectively (242). Clinafloxacin (200 mg every 12 h) was reported to produce a more than doubling of serum theophylline concentration in one case report (241). Finally, grepafloxacin (600 mg every day) has been reported to increase the  $C_{\max}$  of theophylline by 82% and to decrease the total theophylline clearance by about 50% (243).

Levofloxacin, moxifloxacin, sparfloxacin and trovafloxacin have not been observed to produce a clinically significant increase in theophylline levels ([242,244–248](#)). If ciprofloxacin or clinafloxacin is administered to a patient on theophylline, theophylline levels should be monitored and the dosage of theophylline adjusted when necessary ([6,241](#)). For concomitant grepafloxacin therapy, the dosage of theophylline should be reduced by 50% and theophylline levels monitored ([243](#)). Monitoring of theophylline levels is not necessary for the other agents when coadministered with theophylline. However, the patient should still be monitored for clinical signs of theophylline toxicity ([13](#)).

### **Warfarin:**

Ciprofloxacin has been reported to decrease the metabolism of warfarin ([6](#)). The possibility of an interaction with warfarin has been investigated for grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin and trovafloxacin ([9,243,250, 251](#)). No alteration in the pharmacokinetics or anticoagulant action of warfarin was reported when it was administered concomitantly with each of these five fluoroquinolones ([9,243,250,251](#)).

### **Phenytoin:**

An interaction between phenytoin and ciprofloxacin has been reported in a few patients. This interaction is thought to be the result of reduced metabolism of phenytoin, caused by fluoroquinolone inhibition of the cytochrome P450 isoenzyme ([6](#)). Studies have not yet been conducted to investigate whether any of the new fluoroquinolones also interact with phenytoin.

### **Drugs prolonging the QT interval:**

In the adverse effects portion of this review, it was noted that grepafloxacin and especially sparfloxacin may cause QTc interval prolongation ([218,222](#)). Torsades de pointes is sometimes

proceeded by marked QT prolongation. Hence, grepafloxacin and sparfloxacin should be used with extreme caution, if at all, in patients taking other medications that are known to prolong the QT interval or induce torsades de pointes ([Table 10](#)) ([249](#)). If these medications are used together, an additive prolongation of the QT interval may result. No reports of torsades de pointes attributed to a drug interaction with grepafloxacin were found in the literature. When sparfloxacin was administered with cisapride (Prepulsid, Janssen-Ortho) in one study, a prolongation of the QTc interval of 7.7% resulted ([129](#)). This is greater than the prolongation of 3% reported for sparfloxacin alone ([222](#)). However, no cardiovascular side effects were noted ([129](#)). Terfenadine has also been reported to produce an additive increase in the QTc interval when taken with sparfloxacin ([222](#)).

TABLE 10 Drugs that have been reported to prolong the QT interval or induce torsades de pointes (potential interaction with grepafloxacin and sparfloxacin)	
Class	Drugs
Antiarrhythmics	
Class Ia	Disopyramide, procainamide, quinidine
Class Ib	Ambucaine, buprenorphine, tocainide
Class III	Ethacrynic acid, sotalol, sotalolol, sotalololol, sotalolololol
Anticancer	Amphotericin, interferon
Antidepressants or antipsychotics	Chlorazepate, haloperidol, meprobamate, pentamidine, quinine
Prokinetic agents	Cisapride
Prokinetic agents	Chlorazepate, haloperidol, lithium, phenothiazines, promazine, tricyclic antidepressants
Others	Amphotericin, probucol, tacrolimus, vasopressin

[TABLE 10](#)

Drugs that have been reported to prolong the QT interval or induce torsades de pointes (potential interaction with grepafloxacin and sparfloxacin)

FORMULARY AND

PHARMACOECONOMIC CONSIDERATIONS

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Of the newer fluoroquinolones discussed, only levofloxacin, grepafloxacin and trovafloxacin are commercially available in Canada. These are in addition to the currently available fluoroquinolones: norfloxacin, ciprofloxacin and ofloxacin. These newer fluoroquinolones differ with respect to spectrum of activity and frequency of administration. Much of the therapeutic focus of the newer fluoroquinolones is on the use of these agents for the treatment of respiratory tract infections, specifically community-acquired pneumonia. Due to the emergence of penicillin-resistant *S pneumoniae* infections, the role of the newer

fluoroquinolones has gained further prominence ([252](#)). The challenge, however, for many practitioners, clinicians, and provincial and hospital formularies is to determine the place and role of these new agents in the environment of emerging antibiotic resistance and economic constraints.

The acquisition cost per day for the quinolone class of agents is listed in [Table 11](#). Factors that should influence the use of these agents include local or regional epidemiology, antibiotic resistance, patterns of prescribing, severity of illness, fluoroquinolone considerations (adverse effects, drug interactions), availability of other antibiotic regimens, patient considerations (compliance, dosing convenience) and patient or payer economic considerations. Other ancillary costs such as intravenous admixture costs may also need to be considered. These must be considered when a fluoroquinolone is reviewed for addition to a provincial or hospital formulary.

Fluoroquinolone	Daily dosage	Acquisition cost per day (\$)
<b>Oral</b>		
Nalidixic acid	400 mg twice daily	4.38
Ofloxacin	200–400 mg twice daily	4.14–4.83
Ciprofloxacin	250–750 mg twice daily	4.44–9.46
Levofloxacin	250–500 mg twice daily	4.44–9.21
Grepafloxacin	600 mg once daily	5.94
Trovafloxacin	100–200 mg once daily	4.21–5.23
<b>Intravenous</b>		
Ciprofloxacin	400 mg in every 12 h	66.00
Levofloxacin	500 mg in every 24 h	40.00
Axastrofloxacin	200–300 mg in every 24 h	42.87–64.15

**TABLE 11**

Cost comparison of commercially available fluoroquinolones in Canada\*

At this time, there is a paucity of published pharmacoeconomic studies of the newer fluoroquinolones. Although pharmacoeconomic evaluations of the new quinolones have been prepared and submitted by the manufacturer (to provincial formularies, health ministries or hospital formularies), these evaluations were not available to us during this review. Past economic analyses with ciprofloxacin, however, have clearly demonstrated the economic benefits of the fluoroquinolone class of antibiotics ([253–255](#)). The majority of these studies have evaluated the role of sequential antibiotic therapy, ie, the conversion of intravenous to oral antibiotic therapy with oral ciprofloxacin in hospitals. Fliegelman and co-workers ([255](#))

estimated a reduction in antibiotic acquisition costs from US\$427 to US\$244/patient while reducing the length of stay by 20%. Paladino and colleagues ([254](#)) reported a reduction in treatment cost and resultant cost savings per patient of US\$293 when intravenous therapy was converted from intravenous to oral. Considerations of these analyses included the drug cost, cost of treatment failures, drug preparation and administration costs as well as adverse effects. A further retrospective cost effectiveness analysis compared ceftazidime with sequential intravenous or oral ciprofloxacin for the treatment of nosocomial pneumonia ([256](#)). Decision analysis found that ciprofloxacin was cost effective compared with ceftazidime.

These findings indicate that the newer fluoroquinolones also offer similar cost benefits when used in sequential oral therapy by decreasing drug therapy costs and potentially decreasing the length of hospital stay for indications studied in the ciprofloxacin trials. Knowledge of the acquisition cost and frequency of administration suggests that the once daily administration of the newer fluoroquinolones may decrease in-patient drug preparation and administration costs while improving patients' out-patient adherence to their antibiotic regimen. However, economic analyses concerning the use of the newer fluoroquinolones for community-acquired pneumonia using Canadian data are not available and cannot be extrapolated from existing studies to the community or out-patient use of these agents.

There is a paucity of data comparing fluoroquinolone with fluoroquinolone. As a result, pharmacoeconomic analysis is often difficult due to a lack of comparative clinical trial data. A report from the Canadian Coordinating Office Health Technology Assessment attempted to evaluate the economics of fluoroquinolones in several indications ([257](#)). However, due to the absence of data and limited assumptions, the economic evaluation was only conducted for a three-day treatment of cystitis ([257](#)).

## CONCLUSIONS

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The new fluoroquinolones offer once daily dosing and a spectrum of activity different from that of existing fluoroquinolones. These differences should be placed in the context of local epidemiology, antibiotic resistance profiles and patterns of antibiotic prescribing (institutional or community). Consideration of the newer fluoroquinolones for a hospital or provincial formulary should take into account the potential economic advantages with respect to dosing, acquisition cost and adverse effects as well as potential for overuse of this class of agents. Nevertheless, the new fluoroquinolones offer a useful addition to our current armamentarium of antibiotics for the institutional and community management of infections.

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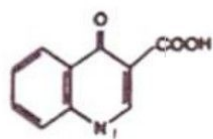
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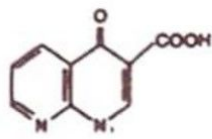
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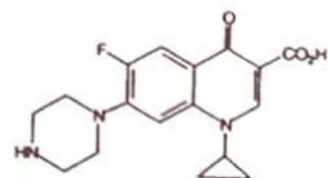
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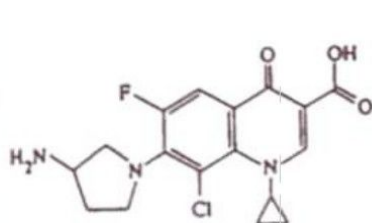
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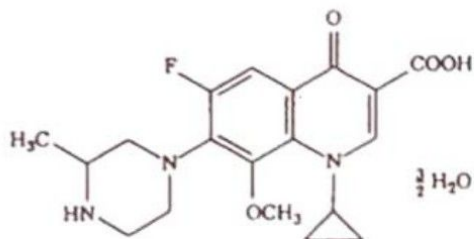
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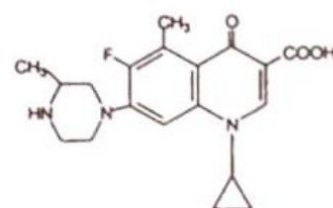
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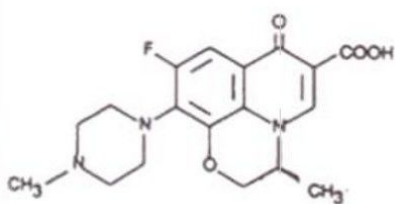
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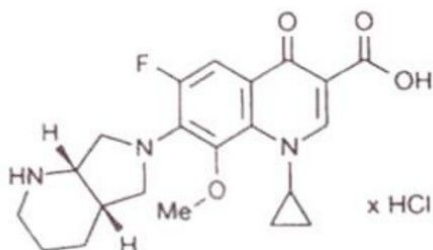
Gatifloxacin



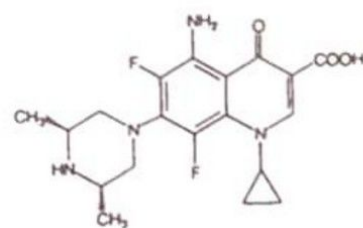
Grepafoxacin



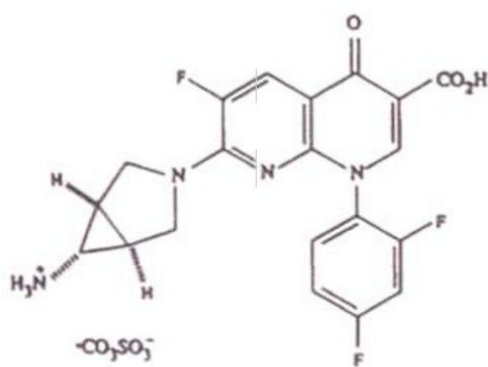
Levofloxacin



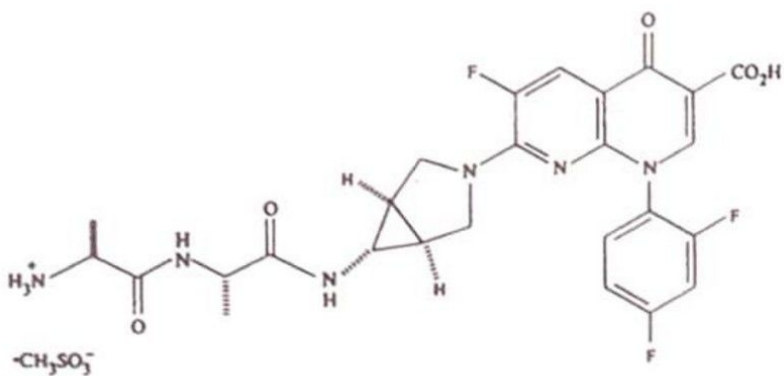
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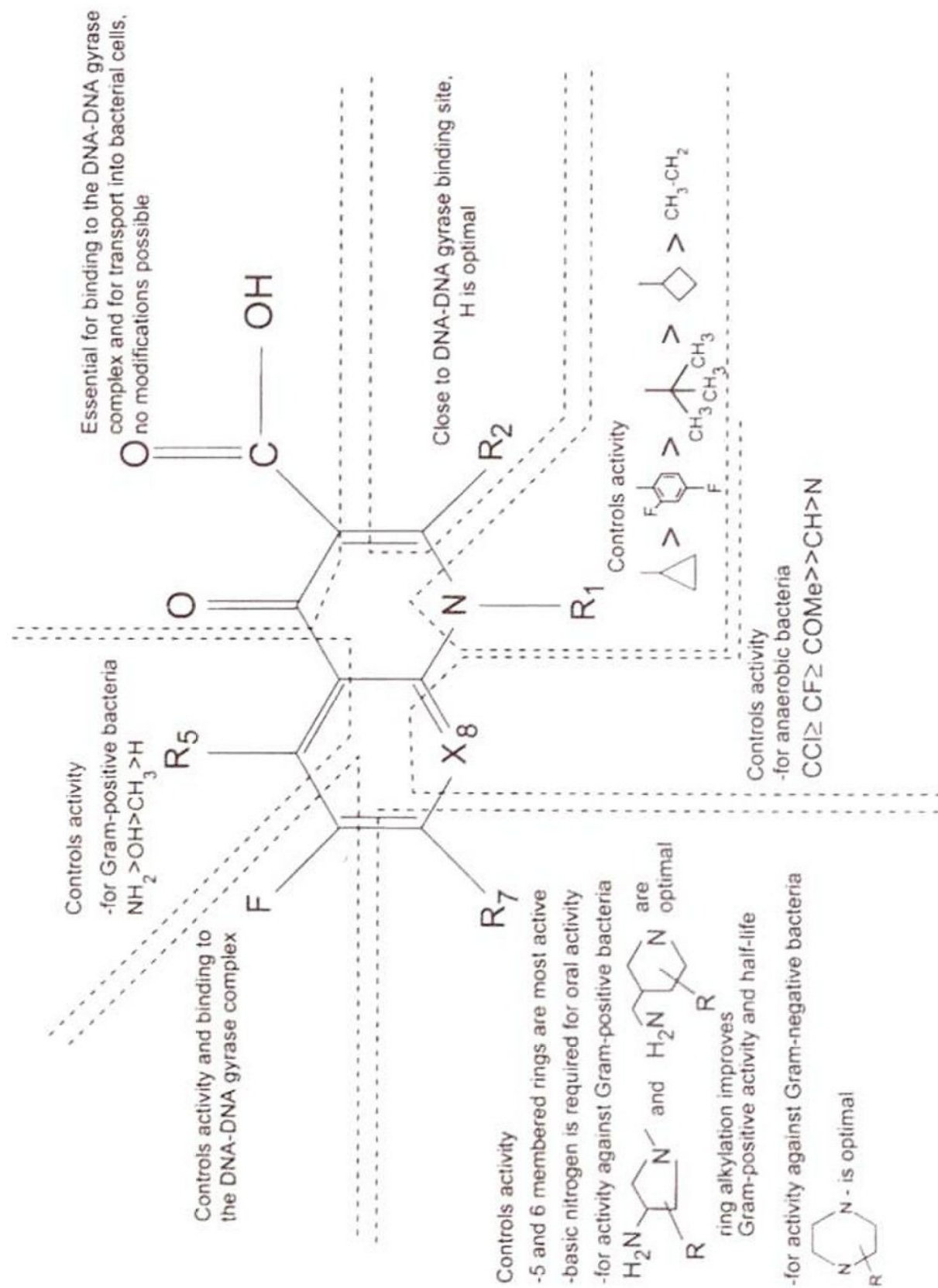
Sparfloxacin



Trovafloxacin



Alatrofloxacin





**TABLE 1**

In vitro activity of the new fluoroquinolones and ciprofloxacin against Gram-positive aerobes

Bacteria	Fluoroquinolones															
	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Grepafloxacin		Levofloxacin		Moxifloxacin		Sparfloxacin		Trovafoxacin	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Staphylococcus aureus</i> (MS)	0.5	1	0.03	0.03	0.1	0.25	0.03	0.12	0.12	0.5	0.06	0.12	0.06	0.12	0.015	0.03
<i>S aureus</i> (MR)	1	16	0.06	0.5	0.2	3.1	4	8	4	16	2	4	0.06	8	0.25	2
<i>Staphylococcus epidermidis</i> (MS)	0.25	1	0.06	0.13	0.1	3.1	0.06	4	0.25	2	0.06	2	0.12	4	0.06	2
<i>S epidermidis</i> (MR)	1	16	0.25	1	0.1	3.1	0.12	4	2	8	1	2	0.12	8	1	4
<i>Staphylococcus sapr ophyticus</i>	0.5	0.5	0.06	0.13	NA	NA	0.12	0.12	NA	NA	0.12	0.25	0.12	0.25	0.03	NA
<i>Streptococcus pyogenes</i>	0.5	1	0.06	0.06	0.25	0.5	0.25	0.25	0.5	0.5	0.25	0.25	0.25	0.5	0.06	0.12
<i>Streptococcus agalactiae</i>	1	2	0.12	0.25	0.25	0.5	0.12	0.5	0.5	1	0.25	0.25	0.25	0.25	0.12	0.25
<i>Streptococcus pneumoniae</i> (PS)	1	2	0.06	0.12	0.25	0.5	0.12	0.25	1	1	0.06	0.12	0.25	0.5	0.06	0.12
<i>S pneumoniae</i> (PR)	1	2	0.06	0.12	NA	NA	0.25	0.25	1	1	0.06	0.12	0.25	0.5	0.06	0.12
<i>Enterococcus faecalis</i>	1	8	0.13	0.5	0.5	1	0.25	2	1	2	0.25	4	0.5	1	0.25	0.5
<i>Enterococcus faecium</i>	4	8	0.5	1	1	8	2	8	2	8	2	8	1	4	0.5	4
<i>Listeria monocytogenes</i>	1	2	0.13	0.13	NA	NA	NA	NA	1	1	0.5	0.5	1	2	0.12	0.25

National Committee for Clinical Laboratory Standards approved and tentative breakpoints ( [42](#)): *S pneumoniae* – grepafloxacin  $\geq 2$   $\mu\text{g/mL}$  is resistant, levofloxacin  $\geq 8$   $\mu\text{g/mL}$  is resistant, sparfloxacin  $\geq 2$   $\mu\text{g/mL}$  is resistant, trovafloxacin  $\geq 4$   $\mu\text{g/mL}$  is resistant, and no data are available for others. *Staphylococcus* species: ciprofloxacin  $\geq 4$   $\mu\text{g/mL}$  is resistant, grepafloxacin  $\geq 4$   $\mu\text{g/mL}$  is resistant, levofloxacin  $\geq 8$   $\mu\text{g/mL}$  is resistant, sparfloxacin  $\geq 2$   $\mu\text{g/mL}$  is resistant, and no data are available for others. MIC<sub>50</sub> Minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> MIC of 90% of isolates; MR Methicillin resistant; MS Methicillin sensitive; NA Information not available; PR Penicillin resistant (penicillin MIC  $\geq 2.0$   $\mu\text{g/mL}$ ); PS Penicillin sensitive. Adapted from references: ciprofloxacin [43–51](#); clinafloxacin [10,43,50,52–55](#); gatifloxacin [11,56–58](#); grepafloxacin [46,59–62](#); levofloxacin [43,44,48,62–67](#); moxifloxacin [14,43,68–71](#); sparfloxacin [11,14,43,44,51,54,57,58,62,65,71–75](#); trovafloxacin [10,43–45,47,49,53,72,76–80](#)

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## TABLE 2

In vitro activity of the new fluoroquinolones against Gram-negative aerobes

Bacteria	Fluoroquinolones															
	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Grepafloxacin		Levofloxacin		Moxifloxacin		Sparfloxacin		Trovafoxacin	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Acinetobacter</i> species	0.25	1	0.03	0.25	0.06	0.5	0.015	4	0.12	0.5	0.06	4	0.015	0.25	0.06	8
<i>Citrobacter freundii</i>	0.03	0.12	0.03	0.12	0.2	0.78	0.06	0.5	0.12	0.5	0.12	1	0.03	0.25	0.06	4
<i>Enterobacter aerogenes</i>	0.015	0.25	0.016	0.5	0.05	0.1	0.03	0.5	0.03	0.06	0.12	0.5	0.06	0.2	0.03	0.12
<i>Enterobacter cloacae</i>	0.015	0.25	0.008	0.016	0.05	0.1	0.03	0.12	0.03	0.2	0.06	0.5	0.015	0.2	0.03	1
<i>Escherichia coli</i>	0.015	0.12	0.015	0.03	0.05	0.1	0.008	0.12	0.05	0.1	0.06	0.5	0.025	0.05	0.03	0.12
<i>Haemophilus influenzae</i>	0.004	0.004	0.004	0.008	0.013	0.025	0.004	0.015	0.015	0.03	0.03	0.06	0.015	0.025	0.015	0.03
<i>Haemophilus influenzae</i> (BLP)	0.004	0.008	NA	NA	NA	NA	0.008	0.008	0.008	0.008	0.03	0.06	0.004	0.004	0.004	0.008
<i>Klebsiella pneumoniae</i>	0.03	0.06	0.016	0.12	0.05	0.1	0.03	0.12	0.06	0.25	0.12	1	0.05	0.12	0.03	0.5
<i>Klebsiella</i> species	0.03	0.25	0.03	0.06	0.06	0.5	0.03	0.06	0.015	0.015	0.06	0.25	0.06	0.25	0.5	1
<i>Moraxella catarrhalis</i>	0.015	0.06	0.008	0.008	0.05	0.05	0.008	0.015	0.03	0.06	0.06	0.12	0.015	0.025	0.008	0.015
<i>Morganella morganii</i>	0.015	0.06	0.015	0.03	0.1	0.25	0.12	0.25	0.06	0.12	0.25	1	0.2	0.4	0.12	0.5
<i>Neisseria gonorrhoeae</i> (PS,PR)	0.004	0.008	0.002	0.004	0.006	0.013	0.008	0.015	0.013	0.2	0.015	0.03	0.004	0.004	0.008	0.015
<i>Neisseria meningitidis</i>	0.004	0.008	NA	NA	0.004	0.008	NA	NA	NA	NA	0.008	0.015	0.001	0.001	0.004	0.008
<i>Proteus mirabilis</i>	0.03	0.06	0.015	0.03	0.2	0.25	0.12	0.5	0.06	0.1	0.25	0.5	0.25	0.5	0.25	0.5
<i>Proteus vulgaris</i>	0.03	0.06	NA	NA	0.12	0.25	0.06	0.5	0.03	0.06	0.25	0.5	0.12	0.5	0.12	0.5
<i>Providencia rettgeri</i>	0.12	1	0.016	0.13	1.56	6.25	0.12	4	0.25	4	NA	NA	0.25	1	0.25	0.5
<i>Providencia stuartii</i>	0.25	1	0.016	0.13	0.2	0.39	0.12	4	0.25	0.5	4	16	0.1	0.5	0.5	2

Bacteria	Fluoroquinolones															
	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Grepafloxacin		Levofloxacin		Moxifloxacin		Sparfloxacin		Trovafoxacin	
	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC	MIC
<i>Pseudomonas aeruginosa</i>	0.25	4	0.25	0.5	2	8	0.5	>4	1	16	2	8	1	8	0.5	8
<i>Burkholderia cepacia</i>	8	32	2	8	NA	NA	NA	NA	8	16	NA	NA	4	32	4	16
<i>Salmonella</i> species	0.015	0.03	0.015	0.03	0.06	0.25	0.015	0.06	0.06	0.06	0.06	0.12	0.03	0.03	0.06	0.06
<i>Serratia marcescens</i>	0.12	2	0.06	0.13	0.78	6.25	0.12	>4	0.25	1	0.25	2	0.5	2	0.25	1
<i>Shigella</i> species	0.015	0.015	0.015	0.03	0.03	0.03	0.008	0.015	0.03	0.03	0.015	0.03	0.008	0.016	0.015	0.03
<i>Stenotrophomonas maltophilia</i>	4	16	0.25	1	0.5	4	NA	NA	2	8	0.25	2	0.5	2	0.25	2
<i>Yersinia enterocolitica</i>	0.015	0.03	0.004	0.008	NA	NA	0.015	0.03	0.03	0.06	0.06	0.12	0.016	0.03	0.06	0.06

National Committee for Clinical Laboratory Standards Approved and tentative breakpoints (42): Enterobacteriaceae – ciprofloxacin  $\geq 4$   $\mu\text{g/mL}$  is resistant, grepafloxacin  $\geq 4$   $\mu\text{g/mL}$  is resistant, levofloxacin  $\geq 8$   $\mu\text{g/mL}$  is resistant, and no data are available for others. BLP Beta-lactamase positive; MIC<sub>50</sub> Minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> MIC of 90% of isolates; NA Information not available; PR Penicillin resistant; PS Penicillin sensitive. Adapted from references: ciprofloxacin 43–46,59,63,80,81; clinafloxacin 10,43,50,52,54,81,82; gatifloxacin 11,56–58; grepafloxacin 46,59,61; levofloxacin 43,44,63,64,67,81,82,84; moxifloxacin 14,43,68–70; sparfloxacin 11,43,44,54,57,58,63,72–75,81; trovafoxacin 10,43–45,47,57,63,76,77,80,81

**TABLE 3**

In vitro activity of the new fluoroquinolones and ciprofloxacin against anaerobes

Bacteria	Fluoroquinolones															
	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Grepafloxacin		Levofloxacin		Moxifloxacin		Sparfloxacin		Trovafoxacin	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Bacteroides fragilis</i>	4	16	0.13	0.5	0.39	1.56	2	16	2	8	0.5	1	2	2	0.25	0.5
<i>B fragilis</i> group	8	32	0.06	0.25	NA	NA	4	8	2	16	0.25	1	2	4	0.5	1
<i>Clostridium difficile</i>	8	16	0.5	2	0.78	1.56	8	32	6.25	6.25	1	2	4	8	1	4
<i>Clostridium perfringens</i>	0.25	1	0.06	0.13	0.39	0.39	0.5	1	0.2	0.39	0.5	0.5	0.25	1	0.12	0.25
<i>Fusobacterium</i> species	1	4	0.06	0.5	NA	0.39	1	8	0.25	4	0.12	0.5	1	2	0.25	2
<i>Peptostreptococcus</i> species	1	2	0.06	0.5	NA	3.13	1	2	0.5	2	0.12	0.25	0.25	0.5	0.06	0.5

National Committee for Clinical Laboratory Standards approved and tentative breakpoints ( [85](#)); anaerobes – trovafoxacin  $\geq 8$   $\mu\text{g/mL}$  is resistant; no data are available for others. MIC<sub>50</sub> Minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> Minimum inhibitory concentration of 90% of isolates; NA Information not available. Adapted from references: ciprofloxacin [10,54,86–90](#); clinafloxacin [10,52,54,91,92](#); gatifloxacin [56–58,92](#); grepafloxacin [59,89,92](#); levofloxacin [83,93,94](#); moxifloxacin [68–70,90,95](#); sparfloxacin [14,54,57,58,75,88,92,93](#); trovafoxacin [10,45,47,83,86,87,92](#)

**TABLE 4**

In vitro activity of the new fluoroquinolones and ciprofloxacin against other clinically important bacteria

Bacteria	Fluoroquinolones															
	Ciprofloxacin		Clinafloxacin		Gatifloxacin		Grepafloxacin		Levofloxacin		Moxifloxacin		Sparfloxacin		Trovafoxacin	
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Chlamydia pneumoniae</i>	1	2	NA	NA	0.063	0.13	NA	0.12	0.25	0.5	1	1	0.063	0.063	1	1
<i>Legionella pneumophila</i>	0.03	0.06	0.008	0.015	NA	NA	0.015	0.015	0.016	0.032	0.015	0.015	0.004	0.004	0.004	0.004
<i>Mycoplasma pneumoniae</i>	1	2	0.016	0.031	NA	0.06	NA	0.5	0.25	0.5	0.06	0.12	0.13	0.13	0.25	0.25
<i>Ureaplasma urealyticum</i>	4	4	0.13	0.25	0.25	0.5	NA	0.5	0.5	1	0.12	0.12	0.25	0.5	0.13	0.5

MIC<sub>50</sub> Minimum inhibitory concentration of 50% of isolates; MIC<sub>90</sub> MIC of 90% of isolates; NA Information not available. Adapted from references: ciprofloxacin [96-99](#); clinafloxacin [98,99](#); gatifloxacin [97,99](#); grepafloxacin [101](#); levofloxacin [97,99,102,103](#); moxifloxacin [70,104,105](#); sparfloxacin [96-98](#); trovafoxacin [96,106,107](#)

**TABLE 5**

Pharmacokinetic parameters of the new fluoroquinolones and ciprofloxacin following a single oral dose

Drug	Dosage (mg) <sup>‡</sup>	% F	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (h)	AUC (mg <sup>*</sup> ·h/L)	T <sub>1/2</sub> (h)	Vd/F (L/kg)	% Protein binding	% Excreted unchanged	Dose adjustment <sup>*</sup>		Ref
										Renal	Hepatic	
Ciprofloxacin	500	70	2.20	1.5	10.0	4.0	3.5	30	30	Yes	No	<a href="#">3,6,106</a>
	750	70	3.00	1.5	14.0	4.0	3.5	30	30	Yes	No	
Clinafloxacin	200	ND	2.10	1.0	10.2	6.1	2.4	50	50	ND	ND	<a href="#">107,108</a>
Gatifloxacin	200	95	1.71	1.8	14.5	7.1	2.3	20	83	ND	ND	<a href="#">109</a>
Grepafloxacin	200	72	0.60	2.0	6.5	11.4	6.5	50	10	No	Yes	<a href="#">110–115</a>
	400	72	1.00	2.0	11.4	11.4	6.5	50	10	No	Yes	
	600	72	1.41	2.0	19.7	11.4	6.5	50	10	No	Yes	
Levofloxacin	500	99	5.30	1.4	48.0	6.7	1.2	31	78	Yes	ND	<a href="#">116–122</a>
	750	99	7.10	1.4	82.0	6.7	1.2	31	78	Yes	ND	
Moxifloxacin	200	86	1.20	1.8	15.3	11.0	3.5 <sup>‡</sup>	48	20	ND	ND	<a href="#">123–125</a>
	400	86	3.10	1.8	30.8	11.0	3.5 <sup>‡</sup>	48	20	ND	ND	
Sparfloxacin	200	90	0.67	4.5	17.0	19.0	4.6	56	10	Yes	No	<a href="#">126–132</a>
	400	90	1.30	4.5	33.0	19.0	4.6	56	10	Yes	No	
Trovafoxacin	100	88	1.1	1.1	11.0	11.0	1.2	73	8	No	No	<a href="#">108,133–138</a>
	200	88	2.2	1.1	27.0	11.0	1.2	73	8	No	No	

\*Dose adjustment refers to whether or not the fluoroquinolone requires any dosage adjustments in patients with impaired renal or hepatic function.

<sup>†</sup>Dosage only applies to peak concentration reached in the plasma/serum (C<sub>max</sub>) and area under the plasma concentration time curve (AUC). The other parameters represent an average of the values available in the literature irrespective of dosage. The dosages reported are based on the dosages commonly used in clinical trials for these drugs.

<sup>‡</sup>Volume of distribution for moxifloxacin was approximated by dividing the literature value of 242 L by 70 kg. F Bioavailability; ND No data; Ref References; T<sub>1/2</sub> Half-life;

T<sub>max</sub> Time to reach C<sub>max</sub>; Vd Volume of distribution



**TABLE 6**

Penetration of the new fluoroquinolones and ciprofloxacin into selected fluids and tissues

Site	Tissue to serum or fluid to serum ratio (reference)				
	Ciprofloxacin (sampling time 1 to 6 h postdose)	Grepafloxacin (sampling time 2 to 5 h postdose)	Levofloxacin (sampling time 1 to 6 h postdose)	Sparfloxacin (sampling time 2 to 6 h post dose)	Trovafloxacin (sampling time 2 to 6 h postdose)
Aqueous humour	0.13 (139)	ND	0.23 (118) <sup>‡</sup>	0.22 (154)	ND
Cerebrospinal fluid	0.37 (106) <sup>*, -</sup>	ND	0.16 (118)	0.25 (154) 0.36 (154) <sup>*, -</sup>	0.2 (155) <sup>‡</sup>
Gall bladder					
Tissue	ND	6.22 (147) <sup>*, -</sup>	1.42 (118,152)	7.1 (154) <sup>*, §</sup>	ND
Bile	5.08 (139)	56.4 (147) <sup>*, -</sup>	5.92 (118,152)	9.6 (154) <sup>¶</sup>	ND
Inflammatory (blister) fluid	1.17 (145)	1.81 (148)	0.96 (153) <sup>*, -</sup>	1.17 (145)	0.64 (156)
Male genital tissues					
Epididymis	ND	4.88 (149)	1.22 (118)	ND	ND
Testis	ND	4.95 (149)	1.63 (118)	ND	ND
Prostate					
Prostatic fluid	2.26 (106)	1.23 (150)	ND	1.5 (154)	ND
Tissue	1.86 (139)	3.60 (149)	1.28 (118)	1.4 (154) <sup>¶</sup>	0.96 (157) <sup>*, -</sup>
Respiratory tract					
Alveolar macrophages	14.3 (146) <sup>*, **</sup>	123.07 (151) <sup>*, -</sup>	ND	41.3 (146) <sup>**, -</sup>	13.32 (158) 24.10 (158) <sup>*, -</sup>
Bronchial mucosa	1.7 (146) <sup>*, **</sup>	2.85 (151) <sup>*, -</sup>	ND	3.3 (146) <sup>**, -</sup>	1.07 (158) 1.12 (158) <sup>*, -</sup>

Tissue to serum or fluid to serum ratio (reference)					
Site	Ciprofloxacin (sampling time 1 to 6 h postdose) <sup>*,**</sup>	Grepafloxacin (sampling time 2 to 5 h postdose) <sup>*</sup>	Levofloxacin (sampling time 1 to 6 h postdose)	Sparfloxacin (sampling time 2 to 6 h post dose) <sup>**</sup>	Trovafloxacin (sampling time 2 to 6 h postdose) <sup>*</sup>
Epithelial lining fluid	1.9 (146) <sup>*,**</sup>	12.30 (151) <sup>*</sup>	ND	11.9 (146) <sup>**</sup>	2.27 (158) <sup>*</sup>
Skin	1.9 (139)	ND	1.14 (118)	1.2 (154)	ND

Specific dosages and sampling times for all of the above data were not provided due to lack of space – see appropriate reference for further details (found in brackets beside values). No data were available for clinafloxacin, gatifloxacin and moxifloxacin, hence they were excluded from this table. Inflammatory fluid to serum ratio was determined by taking the ratio of the area under the plasma concentration time curve values (sampling time not applicable). All others were determined by taking the ratio of tissue concentration to serum concentration (or the ratio of the mean tissue concentration to the mean serum concentration).

\* Multiple doses of the fluoroquinolone were administered to subjects before sample was taken. All other data were collected after a single administration of the study drug.

† Sampling time of 2 to 9 h postdose.

‡ Sampling time of 1 to 24 h postdose.

§ Sampling time of 18 h postdose.

¶ Sample taken at peak concentration reached in the plasma/serum ( $C_{max}$ ) (time not specified in reference).

\*\* Sampling time not specified. ND No data

TABLE 7.1

Results of clinical trials involving clinafloxacin

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
Respiratory tract infections						
Lode (161)	Prospective, randomized, open	166 (136)	Nosocomial pneumonia	C: 200 mg every 12 h (route not specified)	NA	C: 46/69 (67%) cure <sup>*</sup> —
				Ceftaz: 2 g intravenous every 8 h	NA	Ceftaz: 43/67 (64%) cure <sup>*</sup> — (no statistical analysis was provided)
Intra-abdominal infections						
Wilson (213)	NA	551 (425)	Intra-abdominal infection	C: 200 mg every 12 h (route not specified)	NA	C: 156/204 (76%) cure <sup>*</sup> —
				Imipenem: 500 mg every 6 h (route not specified)	NA	Imipenem: 158/221 (71%) cure <sup>*</sup> —(regimens are ‘equivalent’ – no statistical analysis was provided)

n () Number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

\*Cure not defined (eg, in terms of total resolution of symptoms or improvement). C Clinafloxacin; Ceftaz Ceftazidime; Duration Length of treatment; NA Information not available

## TABLE 7.2

Results of clinical trials involving gatifloxacin

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
<b>Genitourinary tract infections</b>						
Suzuki K et al ( <a href="#">190</a> ) (Abst)	Noncomparative, open	11 (11)	Chronic bacterial prostatitis	Gatifloxacin: 200 mg oral bid	14 days	Overall clinical efficacy <sup>*</sup> : Gatifloxacin 10/11 (91%) Two to four week follow-up: relapse rate 3/9 (33%)

n () is the number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

\*Efficacy determined as 'good' or 'excellent' by the clinical investigator . Duration Length of treatment

## TABLE 7.3

Results of clinical trials involving grepafloxacin

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
<b>Respiratory tract infections</b>						
Chodosh et al (162)	Prospective, randomized, double-blind	624 (467)	Acute bacterial exacerbations of chronic bronchitis	G: 400 mg oral every day (n=151)	10 days	3- to 5-day post-treatment success rates <sup>*</sup> G (400 mg): 140/151 (93%) [95% CI=— 4.5% to 8.9%] (Clinically , G regimen is “as effective” as ciprofloxacin regimen) <sup>±</sup>
				G: 600 mg oral every day (n=156)	10 days	G (600 mg): 137/156 (88%) [95% CI=— 10.0% to 4.4%] (Clinically , G regimen is “as effective” as ciprofloxacin regimen) <sup>±</sup>
				Ciprofloxacin: 500 mg oral bid (n=160)	10 days	Ciprofloxacin: 146/160 (91%)
Langan et al (163)	Prospective, randomized, double-blind	656 (611)	Acute bacterial exacerbations of chronic bronchitis	G: 400 mg oral every day (n=202)	7 or 10 days	14- to 28-day post-treatment success rates <sup>±</sup> G (400 mg): 124/143 (87%) [95% CI=— 1.7% to 15.4%] (Clinically , G regimen is “as effective” as ciprofloxacin regimen) <sup>±</sup> G (600 mg): 122/151 (81%) [95% CI=— 7.5% to 10.3%] (Clinically , G regimen is “as effective” as ciprofloxacin regimen) <sup>±</sup> Ciprofloxacin: 123/154 (80%)
						14-day post-treatment success rates <sup>*</sup>
						G (400 mg): 165/202 (82%) [95% CI=— 9.5% to 4.6%] (Clinically , G regimen is “as effective” as amoxicillin regimen) <sup>±</sup>

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
				G: 600 mg oral every day (n=206)	7 or 10 days	G (600 mg): 175/206 (85%) [95% CI=6.2% to 7.5%] (Clinically , G regimen is “as effective” as amoxicillin regimen) <sup>‡</sup>
				Amoxicillin: 500 mg oral tid (n=203)	7 or 10 days	Amoxicillin: 172/203 (85%)  Clinical efficacy <sup>§</sup>
Kobayashi et al (164) (Abst)	Double-blind	203 (190)	Chronic bronchitis (n=90), bronchiectasis with infection (n=53), dif fuse panbronchiolitis (n=6), secondary infection with chronic respiratory disease (n=41)	G: 300 mg oral every day	14 days	G: 84/93 (90%)
				Oflox: 200 mg oral tid	14 days	Oflox: 88/97 (91%) [90% CI=−6.3% to 7.6%] (G regimen is “equivalent” to oflox regimen in “clinical usefulness”) <sup>‡</sup>
						28- to 42-day post-treatment success rates <sup>*</sup>
O’Doherty et al (165)	Prospective, randomized, double-blind	264 (225)	Community-acquired pneumonia	G: 600 mg oral every day	7 or 10 days	G: 87/114 (76%) [95% CI=−12% to 10%] (Clinically , G regimen “is equivalent” to amoxicillin regimen) <sup>‡</sup>
				Amoxicillin: 500 mg oral tid	7 or 10 days	Amoxicillin: 85/111 (77%)
Patel et al (166) (Abst)	Prospective, randomized, double-blind	494 (419)	Community-acquired pneumonia	G: 600 mg oral every day	10 days	G: 175/211 (83%) cure <sup>¶</sup>
				Clarithro: 250 mg oral bid	10 days	Clarithro: 184/208 (88%) cure <sup>¶</sup> (regimens are “equivalent” by a 95% CI calculation, not provided) <sup>‡</sup> Clinical efficacy <sup>§</sup>



Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
Kobayashi et al (167) (Abst)	Double-blind	NA (225)	Bacterial pneumonia (n=195), mycoplasma pneumonia (n=27), chlamydia pneumonia (n=3)	G: 300 mg oral every day Oflox: 200 mg oral tid	14 days 14 days	G: 108/112 (96%) Oflox: 105/113 (93%) [90% CI=−2.3% to 7.5%] (G regimen is “equivalent” to oflox regimen in “clinical usefulness”) ‡
<b>Genitourinary tract infections</b>						
Hook et al (191)	Randomized, open	351 (299) all males	Uncomplicated gonorrhea	G: 400 mg oral single dose Cefixime: 400 mg oral single dose	Single dose Single dose	At 5 to 10 days post-treatment G: 147/149 (99%) cure ** Cefixime: 145/150 (97%) cure **
Matsuda et al (192) (Abst)	Double-blind	244 (201)	Intrauterine infection (n=83), adnexitis (n=63), Bartholin's abscess (n=54)	G: 300 mg oral every day Oflox: 200 mg oral tid	7 days 7 days	Clinical efficacy § G: 98/100 (98%) Oflox: 94/101 (93%) [90% CI=−0.8% to 8.7%] (regimens are “equivalent” in “clinical usefulness”) ‡
Mroczkowski et al (193)	Open, noncomparative, dose ranging study	25 (21) all females	<i>Chlamydia trachomatis</i> infection	G: 400 mg oral every day	7 days	<i>C trachomatis</i> culture was negative at follow-up for all patients (100% cure) (21–28 days)
<b>Skin and skin structure infections</b>						
Arata et al (207) (Abst)	Double-blind	227 (209)	Furuncle, furunculosis, carbuncle, cellulitis, erysipelas	G: 200 mg oral every day	7 days	Clinical efficacy § G: 95/105 (90%)

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
				Oflox: 200 mg oral tid	7 days	Oflox: 92/104 (88%) (regimens reported to be “equivalent”, a CI was not provided) <sup>‡</sup>

n () Number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment). Where n appears under regimen or indication, it refers to the number of clinically evaluable patients that received the treatment or had the condition.

\* Success defined as cure (complete resolution of signs and symptoms of acute infection) or improvement (a reduction in the severity or number of signs and symptoms).

<sup>†</sup>P not reported.

<sup>‡</sup>Success defined as persistent resolution (condition is as good or better than at the end of treatment) or mild relapse (not quite as good as at the end of treatment).

<sup>§</sup>Clinical efficacy not defined.

<sup>¶</sup>Clinical cure not defined.

\*\* Cure defined as microbiological eradication. Clarithro Clarithromycin; Duration Length of treatment; G Grepafloxacin; Oflox Ofloxacin

## TABLE 7.4

Results of clinical trials involving levofloxacin

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
<b>Respiratory tract infections</b>						
DeAbate et al ( <a href="#">168</a> )	Prospective, randomized, open	492 (451)	Acute exacerbation of chronic bronchitis	L: 500 mg oral every day	Mean of 7 days	5 to 7 day post-treatment success rates <sup>*</sup> L: 210/222 (95%)
				Cef ax: 250 mg oral bid	Mean of 10 days	Cef ax: 212/229 (93%) (CI was not provided, but was calculated and therapeutic equivalence reported) <sup>‡</sup>
						5 to 14 day post-treatment cure rates <sup>‡</sup>
Shah et al ( <a href="#">169</a> ) (Abst)	Prospective, randomized, double-blind	839 (427)	Acute exacerbation of chronic bronchitis	L: 250 mg oral every day	7 to 10 days	L (250 mg): 121/156 (78%)
				L: 500 mg oral every day	7 to 10 days	L (500 mg): 108/137 (79%)
				Cef ax: 250 mg oral bid	7 to 10 days	Cef ax: 88/134 (66%) (regimens are “at least equivalent” – no statistical analysis provided) <sup>‡</sup>
Habib et al ( <a href="#">170</a> )	Prospective, randomized, non- blinded	373 (309)	Acute exacerbation of chronic bronchitis	L: 500 mg oral every day	5 to 7 days	L: 141/154 (92%) success <sup>§</sup>
				Cefaclor: 250 mg oral tid	7 to 10 days	Cefaclor: 142/155 (92%) success <sup>§</sup>

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
						[95% CI=-6.5% to 6.6%] (L is “as effective” as cefaclor) <sup>±</sup>
						5 to 7 day post-treatment success rate <sup>±</sup>
File et al (171)	Prospective, randomized, open	590 (456)	Community-acquired pneumonia	L: 500 mg iv or oral every day A: ceftriaxone 1 or 2 g iv every day or bid or cef ax 500 mg oral bid and iv , or oral erythromycin (500 mg to 1 g every 6 h) or doxycycline if atypical pathogens suspected Patient could be switched from iv to oral at investigator’s discretion	Mean of 11.7 days  Mean of 11.7 days	L: 217/226 (96%)  A: 207/230 (90%)
						[95% CI=-10.7% to -1.3%] (levofloxacin “is superior” to the alternative treatment) <sup>±</sup>
						2 to 10 day post-treatment cure rates <sup>±</sup>
Carbon et al (172) (Abst)	Prospective, randomized, double-blind	516 (439)	Community-acquired pneumonia	L: 500 mg oral every day  L: 500 mg oral bid  Amox/clav: 500/125 mg oral tid	7 to 10 days  7 to 10 days  7 to 10 days	L (every day): 138/145 (95%)  L (bid): 137/146 (94%)  Amox/clav: 141/148 (95%) (regimens are “at least equivalent” by a 95% CI analysis, not provided) <sup>±</sup> Clinical efficacy rates <sup>**</sup>
Shishido et al (173) (Abst)	Prospective, randomized, double-blind, noncomparative	10 (10)	Diffuse panbronchiolitis (n=5) or bronchiectasis (n=5)	L: 100 mg oral tid (n=5)  L: 200 mg oral tid (n=5)	Mean of 10 days  Mean of 10 days	L (100 mg): 2/5 (40%)  L (200 mg): 4/5 (80%)  Clinical efficacy rate <sup>±±</sup>

Author (reference)	Design	n ( )	Indication	Regimen	Duration	Results
Nakamori et al (174) (Abst)	Prospective, open, noncomparative	12 (12)	Bronchitis (n=6), dif fuse panbronchiolitis (n=2), bronchiectasis (n=1), bronchial asthma (n=3)	L: 200 mg oral every day	7 to 14 days	L: 12/12 (100%)  Clinical efficacy rate $\pm$
Kawai (175) (Abst)	Prospective, open, noncomparative	16 (14)	Bronchopneumonia (n=12), lung abscess (n=1), dif fuse panbronchiolitis (n=1)	L: 200 mg oral tid	2 to 17 days	L: 14/14 (100%)  Clinical efficacy at day 3 $\pm$
Sato et al (176) (Abst)	Prospective, open, noncomparative	87 (51)	Acute bronchitis (n=18), pneumonia (n=18) or sec infect (n=15)	L: 100 mg oral tid (out-patients) or 200 mg oral tid (in- patients)	3 days out- patients 7 days in- patients	Acute bronchitis 15/18 (83%), pneumonia 16/18 (89%), sec infect 12/15 (80%)
<b>Genitourinary tract infections</b>						
Richard et al (195) (Abst)	Two randomized multicentre studies (pooled results)	259 (NA)	Acute pyelonephritis	L: 250 mg oral every day  Cipro: 500 mg oral bid  Lome: 400 mg oral every day	10 days 10 days 14 days	L: 93% success $\pm$ Cipro: 95% success $\pm$ Lome: 95% success $\pm$ (regimens are “therapeutically equivalent” – no statistical calculation provided) $\pm$  5 to 9 day post-treatment success $\pm$
Klimberg et al (196)	Prospective, open, randomized	461 (336)	Complicated urinary tract infection	L: 250 mg oral every day	Mean of 10 days	L: 159/171 (93%)

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
				Lome: 400 mg oral every day	Mean of 14 days	Lome: 146/165 (88%) Levofloxacin is “as effective” as lomefloxacin (95% CI not provided) <sup>–</sup> Clinical success rate <sup>§§</sup>
Suzuki et al (197) (Abst)	Prospective, open, noncomparative	28 (28)	Nonchlamydial chronic prostatitis	L: 100 mg oral tid or 200 mg oral bid	Mean 13.1 days	L: 21/28 (75%)
<b>Skin and skin structure infections</b>						
Nicodemo et al (208)	Prospective, randomized	272 (253)	Abscess, impetigo, furuncle, cellulitis, pyoderma and other uncomplicated infections	L: 500 mg oral every day Cipro: 500 mg oral bid	7 days 10 days	L: 124/129 (96%) success <sup>§</sup> Cipro: 116/124 (94%) success <sup>§</sup> [95% CI=–8.4% to 3.3%] Levofloxacin is “as effective” as ciprofloxacin 2 to 7 day post-treatment success <sup>–*</sup>
Nichols et al (209)	Prospective, open, randomized	469 (375)	Skin and skin structure infections (cellulitis was most common [47%])	L: 500 mg oral every day Cipro: 500 mg oral bid	Mean of 9.0 days Mean of 9.6 days	L: 178/182 (98%) Cipro: 182/193 (94%) [95% CI=–7.7% to 0.7%]. <sup>†</sup> Levofloxacin is “as effective” as ciprofloxacin

n () Number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment). Where n appears under regimen or indication, it refers to the number of clinically evaluable patients that received the treatment or had the condition.

\*Success defined as cure (complete resolution of signs and symptoms) or improvement (incomplete resolution).

†P not reported.

‡Cure determined by clinical response.



<sup>§</sup>Success defined as cure or improvement.

<sup>¶</sup>Success defined as cure (resolution of signs and symptoms associated with active infection along with improvement in chest roetgenogram findings) or improvement (incomplete resolution of signs, symptoms and chest roetgenogram findings).

<sup>\*\*</sup>Clinical ef ficacy was rated as “excellent” or “good”. A basis for this rating (ie, evaluation of signs and symptoms) was not provided.

<sup>††</sup>Clinical ef ficacy was rated as “excellent” or “good”, based on an assessment of clinical signs and symptoms, and laboratory results.

<sup>‡‡</sup>Clinical ef ficacy was rated as “excellent” or “good”, based on an assessment of clinical symptoms, laboratory results and chest x-rays.

<sup>§§</sup>A definition of clinical success was not provided. A Alternative treatment of   fered; Amox/clav Amoxicillin/clavulanic acid; Cef ax Cefuroxime axetil; Cipro Ciprofloxacin; Duration Length of treatment; iv Intravenous; L Levofloxacin; Lome Lomefloxacin; NA Information not available; Sec infect Secondary infection in patients with chronic respiratory disease

## TABLE 7.5

Results of clinical trials involving sparfloxacin

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
<b>Respiratory tract infections</b>						
DeAbate et al (177) (Abst)	Prospective, randomized, double-blind	798 (504)	Acute bacterial exacerbations of chronic bronchitis	S: 400 mg oral on day 1 then 200 mg oral every day	10 days	S: 216/253 (85%) success <sup>*</sup>
				Oflox: 400 mg oral every 12 h	10 days	Oflox: 223/251 (89%) success <sup>*</sup> [95% CI –9.3% to 2.4%] (regimens are “statistically equivalent”) <sup>±</sup> End of treatment success <sup>±</sup>
Allegra et al (178)	Prospective, randomized, double-blind	734 (351)	Acute exacerbations of chronic obstructive pulmonary disease	S: 200 mg oral on day 1 then 100 mg oral every day	Mean of 10 days	S: 151/173 (87%)
				Amox/clav: 500/125 mg oral tid	Mean of 10 days	Amox/clav: 158/178 (89%) [90% CI=–4.2% to 7.2%] (The S regimen is “as effective” as the amox/clav regimen) <sup>±</sup> 10 day post-treatment success rates <sup>±</sup> S: 129/164 (79%) Amox/clav: 130/163 (80%) [90% CI=–6.3% to 8.5%] (The S regimen is “as effective” as the amox/clav regimen) <sup>±</sup> Overall efficacy
Taytard et al (179) (Abst)	Prospective, randomized, double-blind	NA (201)	Acute bacterial exacerbations of chronic bronchitis	S: 400 mg oral on day 1 then 200 mg oral every day	5 days	S: 86%
				Amox/clav: 500/125 mg tid	10 days	Amox/clav: 85% (a statistical analysis of these results was not provided) <sup>±</sup> End of treatment success <sup>§</sup>

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
Lode et al (180)	Prospective, randomized, double- blind	808 (620)	Community-acquired pneumonia	S: 400 mg oral on day 1 then 200 mg oral every day  Amox/clav: 500/125 mg oral tid  Erythro: 1 g oral bid	Mean of 9.5 days  Mean of 9.5 days  Mean of 9.5 days	S: 269/310 (87%)  Amox/clav: 121/152 (80%) [90% CI=−13.4% to −0.9%] (The S regimen is “at least as ef fective” as the amox/clav regimen) ±  Erythro: 135/158 (85%) [90% CI=−6.9% to 4.3%] (The S regimen is “at least as ef fective” as the erythro regimen) ±  42 day post-treatment success rates § S: 239/285 (84%) Amox/clav: 104/139 (75%) [90% CI=−16% to −2%] (The S regimen is “at least as ef fective” as the amox/clav regimen) ± Erythro: 109/132 (83%) [90% CI=−7.8% to 5.2%] (The S regimen is “at least as ef fective” as the amox/clav regimen) ±
Bensch et al (181) (Abst)	Prospective, randomized, double- blind	428 (338)	Community-acquired pneumonia	S: 400 mg oral on day 1 then 200 mg oral every day  Erythro: 500 mg oral every 6 h	10 days  10 days	S: 153/177 (86%) success ¶  Erythro: 130/161 (81%) success ¶ [95% CI=−2.2% to 13.6%] (regimens are “statistically equivalent”) ±
Donowitz et al (182) (Abst)	Prospective, randomized, double- blind	330 (262)	Community-acquired pneumonia	S: 400 mg oral on day 1 then 200 mg oral every day  Cefaclor: 500 mg oral every 8 h	10 days  10 days	S: 116/134 (87%) success ¶  Cefaclor: 108/128 (84%) success ¶ [95% CI=−6.3% to 10.7%] (regimens are “statistically equivalent”) ±  4- to 7-day post-treatment success §

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
Ortqvist et al (183)	Prospective, randomized, double-blind	304 (264)	Community-acquired pneumonia	S: 400 mg oral on day 1 then 200 mg oral every day ROXI: 150 mg oral bid	Mean of 10.2 days Mean of 10.1 days	S: 124/131 (95%) ROXI: 106/133 (80%) [90% CI=-21.5% to -8.4%] (“sparfloxacin was superior”) $\pm$ 42-day post-treatment success $\pm$ S: 121/129 (94%) ROXI: 103/131 (79%) [90% CI=-22.0% to -8.3%] (“sparfloxacin was superior”) $\pm$ End of treatment success $\text{---}^{**}$
Portier et al (184)	Prospective, randomized, double-blind	213 (167)	Community-acquired pneumonia	S: 400 mg oral on day 1 then 200 mg oral every day Amox/oflox: amox 1 g oral tid and oflox 200 mg oral bid	Mean of 10 days Mean of 10 days	S: 79/86 (92%) Amox/oflox: 66/81 (81%) [90% CI=-19% to -1.8%] (The S regimen is “at least as effective” as the amox/oflox regimen) $\pm$ 30 day post-treatment success rates $\text{---}^{**}$ S: 69/79 (87%) Amox/oflox: 61/78 (78%) [90% CI=-19% to 0.7%] (The S regimen is “at least as effective” as the amox/oflox regimen) $\pm$ End of treatment success $\text{---}^{\pm\pm}$
Aubier et al (185)	Prospective, randomized, double-blind	329 (286)	Community-acquired pneumonia	S: 400 mg oral on day 1 then 200 mg oral every day	Mean of 10.8 days	S: 125/136 (92%)

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
				Amox: amox 1 g oral tid	Mean of 10.8 days	Amox: 131/150 (87%) [90% CI=-10.5% to 1.3%] (The S regimen is at least “as effective” as the amox regimen) <sup>±</sup> 39 to 41 day post-treatment success <sup>±±</sup> S: 112/126 (89%) Amox: 118/140 (84%) [90% CI=-11.4% to 2.2%] (The S regimen is at least “as effective” as the amox regimen) <sup>±</sup>
<b>Genitourinary tract infections</b>						
Moi et al (198)	Prospective, randomized, double-blind	238 (184) all males	Acute gonococcal urethritis	S: 200 mg oral single dose	Single dose	Less than 15 day post-treatment success <sup>±±</sup> S: 95/96 (99%)
				Cipro: 250 mg oral single dose	Single dose	Cipro: 86/88 (98%) [90% CI=-4.4% to 1.9%] (regimens are “equally effective”) <sup>±</sup> 2- to 5-day post-treatment success <sup>§§</sup>
Phillips et al (199)	Prospective, randomized, double-blind	725 (608) all males	Nongonococcal urethritis	S: 200 mg oral on day 1 then oral 100 mg every day	3 days	S (3 day): 159/195 (82%)
				S: 200 mg oral on day 1 then 100 mg oral every day	7 days	S (7 day): 161/201 (80%)
				Doxy: 200 mg oral every day	7 days	Doxy: 174/212 (82%) 14 to 18 day post-treatment success <sup>¶¶</sup> S (3 day): 113/186 (61%) S (7 day): 112/183 (61%) Doxy: 121/196 (62%) (90% CI were calculated but not given. Overall success was “statistically equivalent” between groups) <sup>±</sup>

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
						4- to 14-day post-treatment success ***
Naber et al (200)	Prospective, randomized, double- blind	686 (477)	Complicated urinary tract infection	S: 200 mg oral on day 1 then 100 mg oral every day  Cipro: 500 mg oral bid	Mean of 11 days  Mean of 11 days	S: 166/235 (71%)  Cipro: 187/242 (77%) [90% CI=0.04% to 13.23%] (The groups “dif fer” with cipro being superior) ‡  15 to 56 day post-treatment success *** S: 148/247 (60%) Cipro: 158/239 (66%) [90% CI=-1.0% to 13.4%] (The groups “dif fer” with cipro being superior) ‡ “Clinical results” were “equivalent” between groups ‡
Iravani et al (201) (Abst)	Prospective, randomized, double- blind	1175 (978) all females	Acute uncomplicated urinary tract infection	S: 400 mg oral single dose  S: 400 mg oral on day 1 then 200 mg oral every day  Cipro: 250 mg oral every 12 h	Single dose  3 days  7 days	S (1 day): 335/360 (93%) success ¶ [95% CI=-0.2% to 9.1%]  S (3 day): 328/355 (92%) success ¶ [95% CI=-0.9% to 8.5%]  Cipro: 233/263 (89%) success ¶
Henry et al (202) (Abst)	Prospective, randomized, open label, observer blind	419 (383)	Acute uncomplicated urinary tract infection	S: 400 mg oral on day 1 then 200 mg oral every day  Oflox: 200 mg oral every 12 h	3 days  3 days	S: 173/187 (93%) success ¶  Oflox: 185/196 (94%) success ¶ [95% CI=-6.8% to 3.1%] Clinical efficacy ‡‡‡
Kawada et al (203) (Abst)	Prospective, open, noncomparative	712 (712)	Uncomplicated UTI (n=79), complicated UTI (n=260), urethritis (n=315), prostatitis (n=58)	S: 100 to 300 mg oral every day	3 to 14 days	Uncomplicated UTI: 79/79 (100%) Complicated UTI: 168/260 (65%) Urethritis: 293/315 (93%) Prostatitis: 46/58 (79%)



Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
						Clinical efficacy <sup>+++</sup>
Matsuda et al (204) (Abst)	Prospective, open, noncomparative	201 (201)	Adnexitis (n=31), endometritis (n=85), cervicitis (n=45), other (n=40)	S: 200 to 300 mg oral every day or bid	7 days	Adnexitis: 30/31 (97%) Endometritis: 80/85 (94%) Cervicitis: 44/45 (98%) Others: 40/40 (100%)
<b>Skin and skin structure infections</b>						
						Clinical success <sup>±</sup>
Lipsky et al (210) (Abst)	Prospective, randomized, double-blind	603 (475)	Skin and skin structure infections	S: 400 mg oral on day 1 then 200 mg oral every day Cipro: 750 mg oral every 12 h	10 days 10 days	S: 90% Cipro: 87% [95% CI=-2.8% to 8.6%] (regimens are “statistically equivalent”) <sup>±</sup> Clinical efficacy <sup>§§§</sup>
Takahashi et al (211) (Abst)	Prospective, open, noncomparative	179 (179)	Various (folliculitis, furuncle, impetigo, erysipelas, subcutaneous abscess plus many others)	S: 100 or 200 mg oral every day or bid	7 or 10 days	S: 155/179 (87%) Clinical efficacy <sup>+++</sup>
Watanabe et al (212) (Abst)	Prospective, open, noncomparative	82 (82)	Various (infected atheroma, wound infection, cellulitis and others)	S: 200 mg oral every day or 300 mg oral every day or 150 mg oral bid	4 to 12 days	S: 71/82 (87%)

n () Number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment). Where n appears under regimen or indication, it refers to the number of clinically evaluable patients that received the treatment or had the condition.

\* Success defined as cure or improvement with eradication or presumed eradication.

† P not reported.

‡ Success defined as cure (return to normal of evaluated symptoms) or improvement (decrease in evaluated symptoms);

§ Success defined as cure (complete resolution of signs and symptoms) and resolution or improvement on chest radiography or clinical improvement (incomplete resolution) and resolution on chest radiography.

¶ Success defined by clinical response.

^^ Success defined as clinical cure (apyrexia plus resolution of all signs and symptoms) and resolution or improvement of radiographic signs, or as clinical improvement (apyrexia plus improvement of signs and symptoms) with resolution or improvement of radiographic signs.

^^ Success defined as radiographic resolution or improvement and clinical cure (absence of baseline symptoms), or radiographic resolution and clinical improvement (absence of chills and fever).

## Success defined as eradication of *Neisseria gonorrhoeae*, clinical cure or improvement (disappearance or improvement of symptoms) and less than 10 polymorphonuclear neutrophils (PMNs) per field (magnification  $\times 1000$ ).

§§ Success defined as clinical cure or clinical improvement less than or equal to 5 PMNs (magnification  $\times 1000$ ), plus the absence of *Chlamydia trachomatis*.

¶¶ Success defined as clinical cure less than or equal to 10 PMNs (must be fewer than at end of treatment visit) and absence of *C. trachomatis*.

\*\*\* Success defined as overall efficacy based on clinical efficacy (resolution of symptoms present at inclusion into study) and bacteriological efficacy (eradication of initial pathogen).

+++ Clinical efficacy evaluated based on changes in symptoms.

+++ Clinical efficacy was rated as “excellent” or “good”, based on findings before and after treatment.

§§§ Clinical efficacy was rated as “excellent” or “good”, based on clinical and bacteriological response pre- and post-treatment. Amox Amoxicillin; Amox/clav Amoxicillin/clavulanic acid; Amox/oflox Amoxicillin/ofloxacin; Cipro Ciprofloxacin; Doxy Doxycycline; Duration Length of treatment; NA Information not available; Oflox Ofloxacin; ROXI Roxithromycin; S Sparfloxacin; UTI Urinary tract infection

## TABLE 7.6

Results of clinical trials involving trovafloxacin

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
<b>Respiratory tract infections</b>						
Niederman et al (186) (Abst)	Prospective, randomized, double-blind	433 (362)	Community-acquired pneumonia	A: 200 mg iv every day followed by T 200 mg oral every day	7 to 14 days	End of treatment success <sup>*</sup> – A/T: 160/178 (90%)
				Ceft: 1 g iv every day followed by cefpo 200 mg oral bid (erythro iv or oral could be added here if atypical pneumonia suspected – dose not specified)	7 to 14 days	Ceft/cefpo: 160/184 (87%) P=0.35 (regimens are “statistically equivalent”) Day 30 of study success <sup>*</sup> – A/T: 137/159 (86%) Ceft/cefpo: 139/169 (82%) P=0.25 (regimens are “statistically equivalent”) End of treatment success <sup>*</sup> –
Sullivan et al (187) (Abst)	Prospective, randomized, double-blind	359 (300)	Community-acquired pneumonia	T: 200 mg oral every day	7 to 10 days	T: 138/144 (96%)
				Clarithro: 500 mg oral bid	7 to 10 days	Clarithro: 147/156 (94%) Day 30 of study success <sup>*</sup> – T: 89% Clarithro: 86% (no CI or P , but regimens are “statistically equivalent”) End of treatment success <sup>†</sup> ±
Mandell et al (188)	Summary of six multicentre, double-	257 (NA)	Community-acquired pneumonia caused	A: 200 mg iv every day (2 trials)	7 to 14 days	A/T: 93%

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
(Abst)	blind, comparative clinical trials		by <i>Streptococcus pneumoniae</i>	T: 200 mg oral every day (4 trials)	7 to 10 days	
				C: ceft or erytho, cipro or ampi/amox, clarithro, cefaclor, amox+erythro (route not specified)	NA	C: 94% Day 30 of study success $\pm$ A/T: 91% C: 88% End to treatment success $\pm^*$
Graham et al (189) (Abst)	Prospective, randomized, Double-blind	267 (191)	Nosocomial pneumonia	A: 300 mg iv every day followed by T 200 mg oral every day Cipro: iv bid followed by oral with or without clinda or metro (no dosage given) Aztreonam or vancomycin could be added to either group for documented <i>Pseudomonas aeruginosa</i> or MRSA, respectively	10 to 14 days 10 to 14 days	A/T: 68/88 (77%) Cipro: 80/103 (78%) Day 30 of study success $\pm$ A/T: 69% Cipro: 68% (no CI or P , but the regimens are “statistically equivalent”)
<b>Genitourinary tract infections</b>						
Hook et al (205)	Prospective, randomized, open, noncomparative, dose ranging study	39 (31)	Uncomplicated gonorrhea	T: 50 mg oral single dose (n=9) T: 100 mg oral single dose (n=12) T: 200 mg oral single dose (n=10)	Single dose	At 5- to 9-days post-treatment T: 100% cure for all three regimens (as defined by post-treatment culture results)  5- to 9-day post-treatment success $\pm$
Jones et al (206)	Prospective, randomized, double-blind	625 (394 clinically evaluable)	Uncomplicated gonococcal urethritis or cervicitis	T: 100 mg oral single dose	Single dose	T: 174/182 (96%)

Author (reference)	Design	n ()	Indication	Regimen	Duration	Results
				Oflox: 400 mg oral single dose	Single dose	Oflox: 208/212 (98%) The regimens produced an “equivalent” clinical response (95% CI calculated, but not reported); P not reported

n () Number of patients (number of patients with complete data at the end of treatment or at follow-up if there was no evaluation at the end of treatment). Where n appears under regimen or indication, it refers to the number of clinically evaluable patients who received the treatment or had the condition.

\* Success defined as cure (resolution of baseline signs and symptoms) or improvement (partial resolution and no further antibiotic therapy required).

† Definition of success (clinical efficacy) was not provided;

‡ Success defined as cure (complete resolution of signs and symptoms) or improvement (incomplete resolution). A Alatr ofloxacin; Amox Amoxicillin; Amp/amox Ampicillin/amoxicillin; C Comparators; Ceftr Ceftriaxone; Cefpo Cefpodoxime; Cipr o Ciprofloxacin; Clarithr o Clarithromycin; Clinda Clindamycin; Duration Length of treatment Erythr o Erythromycin; iv Intravenous; Metr o Metronidazole; MRSA Methicillin-resistant Staphylococcus aureus; NA Information not available; Oflox Ofloxacin; T T rova ofloxacin

**TABLE 8**

Frequently occurring adverse effects of the new fluoroquinolones and ciprofloxacin

Adverse effect	Fluoroquinolone							
	Ciprofloxacin	Clinafloxacin	Gatifloxacin	Grepafloxacin	Levofloxacin	Moxifloxacin	Sparfloxacin	Trovafoxacin
Gastrointestinal								
Nausea	<u>±</u>	<u>ND</u>	<u>±</u>	<u>++</u>	<u>±</u>	<u>++</u>	<u>±</u>	<u>++</u>
Vomiting	<u>±</u>	<u>ND</u>	<u>ND</u>	<u>±</u>	<u>+/-</u>	<u>+/-</u>	<u>±</u>	<u>±</u>
Diarrhea	<u>±</u>	<u>++</u>	<u>±</u>	<u>±</u>	<u>±</u>	<u>++</u>	<u>±</u>	<u>±</u>
Central nervous system								
Dizziness	<u>±</u>	<u>ND</u>	<u>±</u>	<u>±</u>	<u>=</u>	<u>+/-</u>	<u>=</u>	<u>+++</u>
Headache	<u>±</u>	<u>ND</u>	<u>±</u>	<u>±</u>	<u>±</u>	<u>+/-</u>	<u>±</u>	<u>±</u>
Allergic								
Rash	<u>±</u>	<u>ND</u>	<u>ND</u>	<u>±</u>	<u>=</u>	<u>+/-</u>	<u>±</u>	<u>+/-</u>
Pruritis	<u>+/-</u>	<u>ND</u>	<u>ND</u>	<u>±</u>	<u>=</u>	<u>+/-</u>	<u>+/-</u>	<u>+/-</u>
Phototoxicity	<u>+/-</u>	<u>++</u>	<u>+/ND</u>	<u>±</u>	<u>+/-</u>	<u>+/-</u>	<u>++</u>	<u>+/-</u>
Cardiovascular (QT c prolongation)* <sup>-</sup>	<u>=</u>	<u>ND</u>	<u>ND</u>	<u>±</u>	<u>=</u>	<u>=</u>	<u>++</u>	<u>ND</u>
Taste perversion	<u>=</u>	<u>ND</u>	<u>ND</u>	<u>+++</u>	<u>+/-</u>	<u>=</u>	<u>=</u>	<u>ND</u>
Injection site reaction	<u>±</u>	<u>±</u>	<u>NA</u>	<u>NA</u>	<u>±</u>	<u>NA</u>	<u>NA</u>	<u>+/-</u>

\*Percentages of patients experiencing this side effect have not been documented for both sparfloxacin and grepafloxacin. The relative number of “+” symbols here only indicates that there are more reports of this side effect with sparfloxacin.

<sup>-</sup>Side effect has not been observed;

<sup>+/-</sup>Side effect occurs in less than 1% of patients;

<sup>+</sup>Side effect occurs in 1% to 5% of patients;

<sup>++</sup>Side effect occurs in 6% to 10% of patients;

<sup>+++</sup>Side effect occurs in more than 10% of patients;

<sup>+/ND</sup>Side effect is expected to occur but has not been documented yet. For clinafloxacin, gatifloxacin, moxifloxacin and trovafoxacin, because these agents have not been extensively studied in clinical trials, if a specific side effect was not found to be reported a ‘ND’ was entered into the table. For ciprofloxacin, grepafloxacin, levofloxacin and sparfloxacin, a ‘-’ was entered into the T able if a specific side ef fect was not found to be reported because these agents have been extensively studied in clinical trials.



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PubMed Central, TABLE 8: Can J Infect Dis. 1999 May-Jun; 10(3): 207-238.

NA Not applicable (fluoroquinolone is not available in an intravenous formulation);

ND No data.

Adapted from references [6](#),[144](#),[145](#),[162–164](#),[166](#),[169](#),[171](#),[190](#),[213](#),[216–224](#)

## TABLE 9

### Drug interactions of the new fluoroquinolones

Interaction with	Fluoroquinolone							
	Ciprofloxacin	Clinafloxacin	Gatifloxacin	Grepafloxacin	Levofloxacin	Moxifloxacin	Sparfloxacin	Trovafloxacin
Metal ion-containing drugs (eg antacids, iron, sucralfate)	Yes	Yes <sup>*</sup>	Yes	Yes <sup>*</sup>	Yes	Yes	Yes	Yes
<i>Mechanism</i>	<i>Chelation resulting in reduced fluoroquinolone bioavailability</i>							
<i>Recommendation</i>	<i>Avoid concomitant administration if possible. Otherwise, administer the fluoroquinolone 2 h before or 6 h after the metal ion containing drug.</i>							
Theophylline <sup>‡</sup>	Yes (+)	Yes (++)/ND	ND	Yes (++)	No	No	No	No
<i>Mechanism</i>	<i>Inhibition of theophylline metabolism, resulting in reduced theophylline clearance</i>							
<i>Recommendation</i>	<i>For ciprofloxacin and clinafloxacin, monitor theophylline levels and adjust theophylline dosage where necessary. For grepafloxacin, reduce theophylline dosage by 50% and monitor theophylline levels. For levofloxacin, moxifloxacin, sparfloxacin and trovafloxacin, monitor for clinical signs of theophylline toxicity.</i>							
Warfarin	Yes/No <sup>‡</sup>	ND	ND	No	No <sup>§</sup>	No	No	No
<i>Mechanism</i>	<i>Reduced metabolism of warfarin</i>							
<i>Recommendation</i>	<i>For ciprofloxacin, monitor prothrombin time or another suitable coagulation parameter.</i>							
Phenytoin	Yes/No <sup>‡</sup>	ND	ND	ND	ND	ND	ND	ND
<i>Mechanism</i>	<i>Reduced metabolism of phenytoin</i>							
<i>Recommendation</i>	<i>For ciprofloxacin, monitor phenytoin levels.</i>							
Drugs prolonging the QT c interval	No	ND	ND	Yes	No	No	Yes	ND
<i>Mechanism</i>	<i>Additive prolongation of the QT c interval</i>							
<i>Recommendation</i>	<i>For grepafloxacin and sparfloxacin, avoid concomitant administration with other drugs known to cause prolongation of the QT c interval.</i>							

\*Theoretical interaction, not actually documented by studies.

<sup>T</sup>For theophylline: + 10% to 50% increase in theophylline peak concentration reached in the plasma/serum ( $C_{\max}$ ) and area under the plasma concentration time curve (AUC), ++ greater than 50% increase in theophylline  $C_{\max}$  and AUC; ++/ND greater than 50% increase in theophylline concentrations, but only one case report has been published on the interaction.

<sup>‡</sup>Interaction has been reported rarely .

<sup>§</sup>Interaction with levofloxacin studied using a single dose of warfarin. ND No data. Adapted from references [6,9,13,129,218,222,233–251](#)

**TABLE 10**

Drugs that have been reported to prolong the QT interval or induce torsades de points (potential interaction with grepafloxacin and sparfloxacin)

<b>Class</b>	<b>Drugs</b>
Antiarrhythmics	
Class Ia	Disopyramide, procainamide, quinidine
Class III	Amiodarone, bretylium, sotalol
Antimicrobials	Erythromycin, trimethoprim/sulfamethoxazole
Antihistamines	Astemizole, terfenadine
Antimalarials or antiprotozoals	Chloroquine, halofantrine, mefloquine, pentamidine, quinine
Prokinetic agents	Cisapride
Psychoactive agents	Chloral hydrate, haloperidol, lithium, phenothiazines, pimozide, tricyclic antidepressants
Others	Amantadine, probucol, tacrolimus, vasopressin

Adapted from reference [249](#)

## TABLE 11

Cost comparison of commercially available fluoroquinolones in Canada<sup>\*</sup>

Fluoroquinolone	Daily dosage	Acquisition cost per day (\$)
Oral		
Norfloxacin	400 mg twice daily	4.36
Ofloxacin	200–400 mg twice daily	4.14–4.83
Ciprofloxacin	250–750 mg twice daily	4.44–9.46
<b>Levofloxacin</b>	250–500 mg once daily	4.44–5.01
<b>Grepafloxacin</b>	600 mg once daily	5.64
<b>Trovafloxacin</b>	100–200 mg once daily	4.21–5.23
Intravenous		
Ciprofloxacin	400 mg iv every 12 h	66.00
<b>Levofloxacin</b>	500 mg iv every 24 h	45.00
<b>Alatrofloxacin</b> <sup>†</sup>	200–300 mg iv every 24 h	42.87–64.15

<sup>\*</sup>Based on manufacturers' listed Canadian price;

<sup>†</sup>Prodrug of trovafloxacin. Bold face indicates a new fluoroquinolone. iv Intravenous