Infect Dis

NO MORE TWIST!:
THE FLUOROQUINOLONES IN THEORY AND PRACTICE

William B. Baine, M.D.

Department of Internal Medicine

Southwestern Medical School

The University of Texas
Southwestern Medical Center at Dallas

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'Twas brillig, and the slithy toves
Did gyre and gimble in the wabe;
All mimsy were the borogroves,
And the mome raths outgrabe.
Lewis Carrol, *Through the Looking-Glass*

Let's twist again, like we did last summer.
Ernest Evans, *Let's Twist Again*

Introduction

Twist ye, twine ye! even so
Mingle shades of joy and woe.
Hope and fear, and peace, and strife,
In the thread of human life.
Sir Walter Scott, *Guy Mannering*

Antibacterial quinolones were first encountered in the process of purifying chloroquine (1, 2). Nalidixic acid was the first 4-quinolone with clinical utility, but the frequency of emergence of resistant strains has severely limited its usefulness even in the treatment of uncomplicated infections of the urinary tract. Still, nalidixic acid has remained an interesting compound because of its hitherto unique mode of action and because of the lack of evidence for plasmid-mediated, hence transmissible, resistance mechanisms (2).

The fluoroquinolones, recently introduced into clinical pratice, represent an important advance in antimicrobial chemotherapy. Norfloxacin and ciprofloxacin, which are currently licensed for use in the United States, as well as other fluoroquinolones have been the subject of several recent reviews and symposia (3-11).

Basic Pharmacology

Turning and turning in the widening gyre
The falcon cannot hear the falconer;
Things fall apart; the center cannot hold....
William Butler Yeats, *The Second Coming*

Nalidixic acid inhibits bacterial DNA synthesis and, at higher concentrations, bacterial synthesis of RNA and protein (12, 13).

DNA gyrase is a member of the class of type II topoisomerases and catalyzes the integration of negative superhelical twists into covalently closed circular DNA and the joining (catenation), which is reversible (decatenation), of loops of DNA as links in a chain. Catenation and decatenation involve DNA cleavage. DNA gyrase is composed of two A and two B subunits, encoded by *gyrA (nalA)* and *gyrB,* respectively. The enzyme is required for DNA replication, repair, and recombination and for the transcription of certain operons (13-17).

Antibacterial potency of a given quinolone correlates with, but is not uniformly proportional to its activity in inhibition of DNA supercoiling by purified DNA gyrase (13).

Evidence exists both for binding of fluoroquinolones to DNA and, conversely, to DNA gyrase. Quinolones may act through the formation of drug-enzyme-DNA complexes that poison DNA gyrase activity instead of merely inhibiting it. Nalidixic acid is a potent inducer of the SOS (RecA) DNA repair system of *Escherichia coli,* suggesting that quinolones probably damage bacterial DNA. Mutants with defects in the SIS system or in the heat-shock protein system may be more susceptible to nalidixic acid than are wild-type bacteria (Hooper).

Quinolones are bactericidal and inhibit DNA synthesis. Although the latter action is not blocked by rifampin and chloramphenicol, these antibiotics do antagonize the antibacterial efficacy of nalidixic acid (13).

Studies of structure-activity relationships have revealed the importance of the 3-carboxyl and 4-oxo groups as well as the effects of substitutions at the N-1, C-6, and C-7 position. Discrepancies between the effects of certain modifications on the antibacterial and gyrase inhibitory activity of certain quinolones suggest that some alterations in antibacterial activity may be mediated through alterations in penetration of the drug into the bacterial cell. Since deep rough (lipopolysaccharide-deficient) mutants of *Salmonella typhimurium* show enhanced susceptibility to nalidixic acid, lipopolysaccharide (LPS) may constitute a barrier to such hydrophobic substances, if not to the newer, hydrophilic, 4-quinolones (13).

Binding of radiolabeled fluoroquinolones to *E. coli* or uptake of drug by bacterial cells does not correlate with relative antibacterial activity. Drug binding or uptake was inhibited by 2,4-dinitrophenol, which dissipates the proton motive force across the cytoplasmic membrane, but not by EDTA, which disrupts the outer membrane (18).

Antibacterial potency appears to be associated with the quinolone nucleus itself. Piperazine substitutions at position 7 introduce activity against *Pseudomonas aeruginosa.* Fluorination is associated with enhanced activity against gram-positive organisms and obligate anaerobes. When studied, differences in antibacterial potency of stereoisomers of a given compound have been noted (2).

The minimal inhibitory concentrations (MICs) of 4-quinolones against *E. coli* and *P. aeruginosa* correlate well with the drug concentrations necessary to achieve 50% inhibition (ID_{50}) of supercoiling activity of DNA gyrase from drug-sensitive strains (19). Although investigations of the mechanisms of action of the 4-quinolones led to the discovery of DNA gyrase, the way in chich the drug inhibits the bacterial enzyme remains to be elucidated. Even less clear is the way in which these drugs actually kill bacterial cells (2).

In addition to inhibiting the catalytic activity of DNA gyrase, quinolone antimicrobials stabilize a gyrase-DNA complex (cleavable complex), which yields DNA double-strand breaks if the protein is denatured. Assays for generation of cleavable complex correlate with those for gyrase inhibition and antimicrobial potency and are relatively sensitive (20).

Subinhibitory concentrations of 4-quinolones can elimnate antimicrobial-resistance and virulence plasmids from bacteria, but the effectiveness of plasmid curing varies as a function of the quinolone, the plasmid, and the bacterial growth medium (21). Ciprofloxacin can eliminate a proportion of plasmids from methicillin-sensitive *Staphylococcus aureus* as well as from gram-negative organisms. Methicillin-resistant *S. aureus* strains do not lose their plasmids upon exposure to ciprofloxacin (22). Elimination of plasmids from bacteria appears to be due to preferential inhibition of plasmid DNA replication or distribution to daughter cells. In order to achieve high levels of plasmid curing, concentrations of drug close to or exceeding the minimal inhibitory concentration (MIC) are required, rendering moot the issue of plasmid propagation (23).

Subinhibitory concentrations of ciprofloxacin induce ultrastructural changes in streptococci and interfere with binding of these bacteria to human buccal mucosal cells in vitro (24).

Subinhibitory concentrations of 4-quinolones induce marked alteration the pattern of bacterial protein synthesis. This observation raises the question of what effects these antimicrobials may have on gene transcription in mammalian cells (2).

Differences among quinolones in potency of inhibition of DNA gyrase do not necessarily correlate with activity shown by these drugs in inhibition of bacterial synthesis of DNA, RNA, or protein (25).

The antibacterial activity of fluoroquinolones is reduced somewhat at high concentrations of Mg^{2+} and, more markedly, at low pH (26).

Clinical Pharmacology

> Once upon a time there were four little
> Rabbits, and their names were--
> Flopsy,
> Mopsy,
> Cotton-tail,
> and Peter.
> Beatrix Potter, *The Tale of Peter Rabbit*

Fluoroquinolones vary in their bioavailability and the extent to which they are metabolized (27). For example, lmost all administered ofloxacin is excreted unchanged by the kidneys, whereas pefloxacin, at the other extreme, undergoes extensive extrarenal metabolism (28). Sensitive high-performance liquid chromatographic assays have been developed for the assay of 4-quinolones (29, 30).

In a reversed-phase thin-layer chromatographic assay with octan-1-ol as the stationary phase most 4-quinolones appear hydrophilic (lipophobic) (31). Fluoroquinolones of intermediate hydrophobicity, such as ofloxacin and pefloxacin, achieve higher serum levels and have a longer half-life of elimination ($t_{½}$) than do more hydrophilic drugs like ciprofloxacin, enoxacin, and norfloxacin (19).

The pharmacokinetics of ciprofloxacin and norfloxacin have been studied in normal volunteers (Table 1) (32).

Table 1. Pharmacokinetic properties of ciprofloxacin and norfloxacin

Site, measurement		Value for indicated drug, dose, and route (mean ±SD)		
		Ciprofloxacin		Norfloxacin
		100 mg iv push	500 mg po	400 mg po
Serum	tmax (h)	NA	1.25 ± 0.5	1.5 ± 0.4
	Cmax (mg/l)	NA	2.3 ± 0.7	1.45 ± 0.1
	$t_{½\beta}$ (h)	4.0 ± 0.9	3.9 ± 0.8	3.25 ± 0.5
Blister fluid	tmax (h)	1.25 ± 1.8	2.6 ± 0.97	2.3 ± 0.4
	Cmax (mg/l)	0.6 ± 0.15	1.4 ± 0.36	1.0 ± 0.3
	$t_{½\beta}$ (h)	4.4 ± 0.6	5.6 ± 2.4	3.5 ± 0.8
Urine	24-h excretion (% of dose)	75.7 ± 10.3	30.6 ± 9.8	27.0 ± 8.6
	C_{12-24h} (mg/l)	6.5	1.9	8.5

Changing the dosing interval of norfloxacin from q12h to q24h has been recommended in patients in whom the creatinine clearance is less than 20 ml/min/1.73 m^2. Eliopoulos suggests that dosage reduction for renal insufficiency may not be necessary during ciprofloxacin therapy unless large doses ($\geq$ 750 mg bid) are used or impairment of drug metabolism is likely (28). Swiss investigators emphasize that the $t_{½\beta}$ of ciprofloxacin is usually little affected by renal failure, although concomitant hypotension, which presumably interferes with hepatic metabolism of the drug, interacts with renal failure and greatly prolongs clearance of this quinolone (33). Nevertheless, Bergan reports that in renal failure the $t_{½}$ for ciprofloxacin is extended from 4 h to 5-10 h (35). Gasser and colleagues advocate reducing the dose of ciprofloxacin by 50% to avoid accumulation of the drug in patients with a creatinine clearance below 50 ml/min (34). Neither ciprofloxacin nor norfloxacin is effectively removed by hemodialysis (28).

The bioavailability of oral ciprofloxacin is 80-85%. Peak serum concentrations occur after 1.2 h, and the drug is 35% protein-bound in serum. After an intravenous dose, 65% is eliminated unchanged, and another 10-15% appears in the form of four metabolites in the urine. Activity against common urinary-tract pathogens is matintained for at least 12 hours after a single dose. Transintestinal elimination accounts for 15% of the dose, which appears in the feces. Although <1% of administered ciprofloxacin appears in the bile, biliary concentrations are comparable to or up to 10 times those in serum. Fecal ciprofloxacin levels reach 200-1000 mg/kg. The drug reaches adequate concentrations in bone, tonsil, intestinal wall, gallbladder, lung, and muscle (35).

Ciprofloxacin is concentrated in tonsillar tissue. Penetration is 45% into saliva and 73-90% into nasal secretions. Levels in aqueous humor are 13-22% of those in serum.. Levels in the vitreous are usually comparable to those in aqueous humor, although absence of detectable drug has been described (36). Levels in sputum and peritoneal fluid (35) and in mesenteric lymph nodes obtained at laparotomy (37) are comparable to those in serum. However, penetration of the drug into bronchial secretions may not always suffice to exceed the MIC of some nosocomial respiratory pathogens (38). Patients with cystic fibrosis have a smaller volume of distribution (2.12 vs. 3.76 l/kg) and shorter serum $t_{\frac{1}{2}\beta}$ (2.62 vs. 3.93 h) than do healthy controls (39). Diarrhea does not reduce serum or fecal ciprofloxacin concentrations, but an apparently idiosyncratic defect in the absorption of ciprofloxacin from the gastrointestinal tract has been reported (40).

The concentration of ciprofloxacin is higher in hepatic bile than in serum and higher in the bile of functioning gallbladders than in hepatic bile (41). Ciprofloxacin is concentrated approximately tenfold in prostatic tissue (35, 42).

Ciprofloxacin reaches levels in cerebrospinal fluid (CSF) that range from 4% of peak plasma levels in normal patients to 15% of peak levels in meningitis (43) For example, in four patients with bacterial or aseptic meningitis given ciprofloxacin, the CSF concenteration of the drug ranged from 0.15 to 0.40 mg/l two to four hours after administration of 500 mg po (44).

Volunteers given intravenous ciprofloxacin, 150 mg/h for 2 h followed by 50 mg/h for 4 h, achieved a mean steady-

state plasma concentration of 0.97 mg/l, with a $t_{1/2}$ of 5.75 ± 0.86 h (45).

Norfloxacin is 15% protein-bound in serum. Urinary levels remain high for at least 12 h. Fecal concentrations are similar to those for ciprofloxacin (35). Norfloxacin reaches higher levels in hepatic bile than in serum and higher levels in the bile of functioning gallbladders than in hepatic bile; nonfunctioning gall bladders are associated with reduced concentrations of norfloxacin in both gallbladder wall and bile (46). Like ciprofloxacin, norfloxacin is concentrated approximately tenfold in prostatic tissue (35).

In renal failure the $t_{1/2}$ of norfloxacin increases from 4.6 h to 5-10 h (35). At 400 mg po bid norfloxacin gives adequate drug concentrations in urine without undue accumulation of drug in patients in whom the creatinine clearance is in the range of 32-48 ml/min/1.73 m^2. Subjects with severe renal impairment (<12 ml/min/1.73 m^2) show no significant accumulation of drug while receiving 400 mg po qd, but concentrations of norfloxacin in urine, while above the MIC for *E. coli*, do not consistently exceed the MIC for *P. aeruginosa* (47).

When theophylline is administered with ciprofloxacin or with most other 4-quinolones, particularly enoxacin, the metabolism of both drugs is retarded, presumably as a result of effects on hepatic enzymes, with elevation of the serum concentration of the bronchodilator (26, 35). Whereas enoxacin produces toxicity in volunteers receiving theophylline, the inhibition of xanthine metabolism is less with ciprofloxacin and nil with norfloxacin or ofloxacin (48, 49).

Magnesium and aluminum hydroxide antacids drastically interfere with intestinal absorption of ciprofloxacin and ofloxacin. Metoclopramide administration accelerates the appearance of peak serum levels of the quinolone. Food and ranitidine delay and slightly diminish intestinal absorption, with delay and diminution in peak serum concentration. The anticholinergic drug pirencepine delays absorption of the quinolone without decreasing its peak serum concentration or the area under the time-concentration curve (26, 35, 50).

Probenecid interferes with active tubular secretion of ciprofloxacin, lowering concentrations of the drug in the

urine without affecting the peak serum concentration or $t_{\frac{1}{2}\beta}$ (26, 35).

Interference with absorption of norfloxacin by concomitantly administered magnesium-aluminum hydroxide suspension has been blamed for persistently positive urine cultures and the development of bacteremia in a patient who was being treated for nosocomial *P. aeruginosa* urinary tract infection (51).

Concentrations of orally or intravenously administered pefloxacin range from 38% to 83% of serum levels in nasal secretions, saliva, sputum, sweat, and tears from patients and volunteers. Pefloxacin administered intraperitoneally to guinea pigs yields concentrations averaging 36-120% of simultaneous serum levels in the aqueous humor, vitreous body, and cerebrospinal fluid of these animals (52). The long half-life of pefloxacin should permit once-daily dosage (53-55). This drug is completely absorbed from the gastrointestinal tract and may undergo enterohepatic circulation in man (56). Absorption of the drug is retarded by a high-fat diet, but without a decrease in bioavailability (57). Cimetidine inhibits nonrenal clearance of pefloxacin, which is extensively metabolized (58).

Like ciprofloxacin, pefloxacin reaches therapeutic levels in bone that commonly exceed those measured in serum (59), and pefloxacin may in fact be more reliably concentrated in bone than are either ciprofloxacin or ofloxacin (60). High concentrations of pefloxacin and ofloxacin are reported from the anterior chamber of the eye (35). Penetration of this drug into CSF is better than with ciprofloxacin, and pefloxacin is also concentrated in brain tissue, particularly in cerebral neoplasms (43). For example, pefloxacin concentrations in normal brain tissue are 44-75% of simultaneous levels in plamsa, and concentrations in tumor specimens reach 1.6 to 3.2 times those measured in healthy tissue (61).

Administration of pefloxacin (62) or ofloxacin (63, 64) to elderly patients for more than two days results in accumulation of the drug unless dosages are reduced.

The concentration of orally administered ofloxacin in prostate and, particularly, in kidney exceeds that in plasma (65). Ofloxacin reaches therapeutic levels in peritoneal fluid in patients undergoing continuous ambulatory peritoneal dialysis (66).

Enoxacin is concentrated over 40-fold above concurrent plasma levels in bronchial mucosa obtained by fiberoptic bronchoscopy (67). In comparison with control subjects, patients with severe burns who receive oral enoxacin display lower peak levels of drug in serum and skin exudates and greater interpatient pharmacokinetic variability (68).

Antibacterial Spectrum In Vitro

> The gyres! the gyres! Old Rocky Face, look forth;
> Things thought too long can be no longer thought,
> For beauty dies of beauty, worth of worth,
> And ancient lineaments are blotted out.
> William Butler Yeats, *The Gyres*

The fluorinated quinolones have a broad antibacterial spectrum *in vitro,* encompassing many strains of Enterobacteriaceae (except for some strains of *Providencia stuartii*) *P. aeruginosa, Acinetobacter, Haemophilus influenzae, Branhamella catarrhalis,* gonococci, meningococci, most bacterial intestinal pathogens (including *Aeromonas, Campylobacter jejuni,* enterotoxinogenic *E. coli, Plesiomonas shigelloides, Salmonella, Shigella* [including nalidixic acid-resistant strains of *S. dysenteriae* type 1], *Vibrio cholerae, V. parahaemolyticus,* and *Yersinia enterocolitica*), *S. aureus, Legionella, Mycobacterium, Rickettsia,* and *Brucella.* Ciprofloxacin is usually the most active drug. Norfloxacin and ofloxacin are least potent against staphylococci *P. cepacia* and particularly *P. maltophilia* are not uniformly susceptible. Activity against *Chlamydia trachomatis* and mycoplasmas is borderline. *Mobiluncus* and *Gardnerella vaginalis,* associated with nonspecific vaginosis, are not sensitive, and most obligate anaerobes, including *Bacteroides fragilis* and most strains of *Clostridium difficile* are resistant, although *B. ureolyticus* and *C. perfringens* may be susceptible (19, 38, 69-71). Although active against a wide range of gram-negative facultative anaerobes and obligate aerobes and against staphylococci the fluoroquinolones have less activity against streptococci, particularly enterococci, but also the pneumococcus (19, 38, 70, 72).

Ciprofloxacin was active *in vitro* against the majority of multiply-resistant gram-negative bacilli isolated from patients in 1985 in a group of hospitals in California. These included isolates of *E. coli,* with the MIC required to inhibit 90% of the strains tested (MIC_{90}) equal to 0.03 mg/l, *Klebsiella pneumoniae* (MIC_{90} = 0.5), *K. oxytoca* (MIC_{90} =

0.03), *Enterobacter cloacae* (MIC_{90} = 0.06), *E. aerogenes* (MIC_{90} = 0.125), *Serratia marcescens* (MIC_{90} = 0.03), *P. aeruginosa* (MIC_{90} = 1), *Proteus vulgaris* (MIC_{90} = 0.03), *P. rettgeri* (MIC_{90} = 1), and *Citrobacter freundii* (MIC_{90} = 0.125) (73). Ninety per cent of strains of *P. aeruginosa* from a community hospital in Michigan have been found to have MICs of ciprofloxacin $\leq$ 0.5 mg/l (74). Ciprofloxacin was the most active of eight quinolone tested in vitro against 400 strains of urinary-tract isolates from Germany (75).

Forty-nine of 50 isolates of *P. aeruginosa* from Australian children were cystic fibrosis were susceptible *in vitro* to ciprofloxacin (76). Ciprofloxacin was more active *in vitro* than enoxacin, norfloxacin, ofloxacin, and CI-934 against gram-negative clinical isolates from Italy, but 9 (8%) of 107 strains of *P. aeruginosa* and 3 (5%) of 56 strains of *P. rettgeri* were ciprofloxacin-resistant (77).

The distribution of MICs of 4-quinolones, aminoglycosides, and β-lactam antibiotics has been studied in clinical strains of *P. aeruginosa.* MICs of ciprofloxacin correlate well with those for other 4-quinolones but less so with MICs of aminoglycosides and not at all with those of β-lactams. For most, but not all strains the minimal bactericidal concentration (MBC) of a 4-quinolone is close to the MIC. Ciprofloxacin-resistant strains selected *in vitro* tend to be more susceptible to aminoglycosides and β-lactams than are the parental strains (78). As in the case of aminoglycosides, inhibition of multiplication of *P. aeruginosa* by fluoroquinolones can be shown to persist for some duration after removal of the antimicrobial from the environment of the bacteria (79).

Ciprofloxacin is more active *in vitro* against *P. aeruginosa* than are ofloxacin and pefloxacin (80), and ciprofloxacin is more active in vitro than norfloxacin, ofloxacin, and imipenem against a wide range of aerobic and facultatively anaerobic gram-negative and gram-positive bacteria (81). Comparison of ciprofloxacin with norfloxacin shows that the former is more active *in vitro* against a variety of bacterial strains, is more effective in the treatment of experimental infections in mice, and is less affected by changes in inoculum size (82).

Strains of *P. maltophilia,* which are increasingly important nosocomial pathogens, are typically resistant to aminoglycosides and beta-lactam antibiotics. Ciprofloxacin and other fluoroquinolones show activity *in vitro* against many such strains (83).

Ciprofloxacin and ofloxacin are less active *in vitro* against *P. aeruginosa* than are piperacillin and ceftazidime (84).

Exposure of *E. coli* and *K. pneumoniae* to ciprofloxacin *in vitro* in a two-compartment model results in rapid bacterial killing. Susceptible strains of *P. aeruginosa* tested in the same model show initial killing, which is succeeded by regrowth of resistant subpopulations (85).

Ciprofloxacin has become an important addition to the available armamentarium for the treatment of infections with methicillin-resistant *S. aureus* and coagulase-negative staphylococci (86-88). Both *S. aureus* and *S. epidermidis* are usually susceptible to ofloxacin and pefloxacin as well (Peters).

Ciprofloxacin is active in vitro against *L. pneumophila,* with MIC and MBC concentrations of 0.024 mg/l. Ciprofloxacin also produces a reduction in bacterial titers in human macrophages infected *in vitro* with *L. pneumophila.* Coadministration of rifampin does not enhance intracellular activity of ciprofloxacin against this organism (89). Charcoal in the agar medium interferes with the activity of quinolones and some other antimicrobials in vitro against *L. pneumophila* (90).

Ciprofloxacin is active *in vitro* against *M. fortuitum* (MIC_{90} = 0.2 mg/l), *M. tuberculosis* (MIC_{90} = 0.8), *M. Kansasii* (MIC_{90} = 1.6), and *M. marinum* (MIC_{90} = 0.8), but isolates of *M. chelonae* and *M. scrofulaceum* are generally resistant (91, 92). Efficacy of ciprofloxacin against experimental infections with *M. fortuitum* and *M. leprae* in mice has been reported (91). *M. avium-intracellulare* strains are variously described as susceptible (93) or resistant (91) to ciprofloxacin *in vitro,* but bactericidal concentrations are higher than those achieved in serum (93).

Of ten strains of *Rhodococcus* tested (not including isolates of *R. equi,* a pulmonary pathogen encountered in patients with acquired immune deficiency syndrome), all were susceptible *in vitro* to ciprofloxacin (92).

Strains of *Nocardia* are variously susceptible (94) or resistant (92) to ciprofloxacin *in vitro.*

Ciprofloxacin is less acitve *in vitro* than erythromycin against *Mycoplasma pneumoniae* and less active than minocycline

against *C. trachomatis, M. hominis,* and *Ureaplasma urealyticum* (95). Both ciprofloxacin and ofloxacin suppress development of inclusion bodies of *C. trachomatis* in cultures of McCoy cells, but these drugs are less active than erythromycin and tetracycline, particularly in preventing the formation of *C. trachomatis* elementary bodies (96).

Ciprofloxacin is additive, indifferent, or, in some reports, antagonistic, but usually not synergistic, with β-lactams against Enterobacteriaceae and *P. aeruginosa.* Ciprofloxacin and aminoglycosides are variously reported to be antagonistic and synergistic against Enterobacteriaceae. Time-kill studies indicated antagonism between ciprofloxacin and chloramphenicol, erythromycin, rifampin, and tetracycline against *E. coli* (97). Some investigators report partial antagonism between fluoroquinolones and aminoglycosides, but not with β-lactam antibiotics (26). Mezlocillin is synergistic *in vitro* with ciprofloxacin against some strains of *K. pneumoniae* and other Enterobacteriaceae (98). Ciprofloxacin shows synergy or indifference in vitro when tested with ceftazidime, mezlocillin, or sisomycin against strains of *Citrobacter, Enterobacter, E. coli, Klebsiella, Proteus, Pseudomonas, Staphylococcus,* and *Streptococcus* (99).

At double the MIC of each drug ciprofloxacin and pefloxacin are more rapidly bactericidal *in vitro* than ceftazidime against *P. aeruginosa* and, unlike methicillin and vancomycin, the 4-quinolones are bactericidal against *S. aureus* (100).

Isolates of urinary-tract pathogens from Austria (101), Egypt (102), and Spain (103) are generally susceptibile to norfloxacin. Norfloxacin is active *in vitro* against a variety of aerobic and facultative potential ocular pathogens except for streptococci. The MIC of two strains of *Moraxella* spp. was 1 mg/l (104).

Ofloxacin was active against a broad range of clinical isolates from Poland; resistance was most common among strains of *P. aeruginosa* and *Enterococcus faecalis* (105). Ofloxacin shows neither synergy nor antagonism when tested *in vitro* with vancomycin against *S. aureus* (106).

Pefloxacin is comparable *in vitro* to norfloxacin and ofloxacin, with good activity against Enterobacteriaceae, *A. hydrophila,* and *A. calcoaceticus.*. Resistance has been noted most commonly among strains of *P. aeruginosa, E. faecalis,* and *Streptococcus pyogenes* (107). This drug is also active against staphylococci (108). Antistaphylococcal activity of

pefloxacin plus vancomycin *in vitro* equals that of the vancomycin alone, rather than that of the more rapidly bactericidal 4-quinolone. Subinhibitory concentrations of rifampin antagonize pefloxacin, whereas the quinolone at levels $\geq$ 0.5 times the MIC prevents the late emergence of rifampin-resistant mutants (109).

Over 99% of 149 isolates of enteric pathogens isolated from patients with diarrhea were susceptibile *in vitro* to fleroxacin (110).

Many additional quinolone antimicrobials, often as yet unnamed, have been developed (72 , 87, 88, 93, 111-115). Some of these are more active in vitro against certain bacterial species than are ciprofloxacin and norfloxacin (94, 116-128).

A-56620 is more active *in vitro* than ciprofloxacin against *Salmonella* spp. (MIC_{90} = 0.06 mg/l), *Campylobacter* spp. (MIC_{90} = 0.12), *S. pneumoniae* (MIC_{90} =1), viridans streptococci (MIC_{90} = 2), and *Bacteroides* spp. (MIC_{90} = 4), but less active against *E. coli, K. pneumoniae, S. marcescens, Pseudomonas* spp., and other gram-negative bacilli (129).

The relative antibacterial potency of two quinolones may vary markedly as a function of the organisms tested. For example, the most active stereoisomer of ciprofloxacin is ten times as active as that of compound S-25930 against *E. coli,* but the latter drug is eight times as potent as the most potent stereoisomer of ciprofloxacin against *S. aureus* (2).

CI-934 is comparable or slightly more active *in vitro* than ciprofloxacin against gram-positive organisms but markedly inferior against gram-negative bacteria (130). Testing of 934 bacterial strains from the M. D. Anderson Hospital against four fluoroquinolones, amikacin, and ceftazidime showed ciprofloxacin to be the most active drug *in vitro* against *A. calcoaceticus, H. influenzae, P. aeruginosa,* and Enterobacteriaceae. CI-934 was equal to ciprofloxacin in activity against *Bacillus cereus* and superior to the other quinolones against *Streptococcus* groups A, B, and G, *E. faecalis, Listeria monocytogenes,* methicillin-sensitive and methicillin-resistant *S. aureus, S. epidermidis, S. haemolyticus, S. hominis,* and *Corynebacterium jeikeium* (JK diphtheroids) (131).

Drug Resistance

> Being young you have not known
> The fool's triumph, nor yet
> Love lost as soon as won,
> Nor the best labourer dead
> And all the sheaves to bind.
> William Butler Yeats, *To a Child Dancing in the Wind*

Single-step mutations to resistance to nalidixic acid and oxolinic acid occur at a frequency of 10^{-6} - 10^{-8}. Although these mutations confer increased MICs to fluoroquinolones, these mutants remain susceptible to clinically achievable concentrations. Single-step mutations that increase the MICs of fluoroquinolones fourfold occur in the range of 10^{-9} or lower, but these mutants are also susceptibile to therapeutic drug concentrations. High-level fluoroquinolone resistance can be produced *in vitro* by serial passage in increasing concentrations of drug (Table 2).

Table 2. Effect of Repeated Subculture of Bacteria in Fluoroquinolones

Organism	MIC before transfers/MIC after transfers (mg/l) Ciprofloxacin	Norfloxacin
E. coli	0.06/ 8	0.06/16
K. pneumoniae	0.12/ 8	0.50/64
P. aeruginosa	0.12/ 2	0.12/16
S. aureus	0.25/64	0.50/64

Such isolates typically show cross-resistance to other

fluoroquinolones and increases in MICs for gram-negative organisms of β-lactam antibiotics as well (Table 3), implying changes in outer membrane permeability (132).

Table 3. Cross-resistance of Fluoroquinolones with β-lactams

Organism, strain	MIC (mg/L) of indicated agent for strain Norfloxacin	Cefotaxime	Moxalactam
E. coli			
parent	0.025	0.025	0.05
mutant	3.1	0.8	0.8
K. pneumoniae			
parent	0.1	0.05	0.1
mutant	6.2	1.6	12.5
E. cloacae			
parent	0.2	0.2	0.2
mutant	100	0.8	3.2

Bacteria resistant to quinolone antimicrobials carry mutations at the *gyrA* and, less commonly, *gyrB* loci or other mutations, including one affecting the OmpF porin, that are thought to affect entry of the drug through the outer membrane of gram-negative organisms. Some of the latter mutations confer pleiotropic drug resistance, as to nalidixic acid, chloramphenicol, and tetracycline (13).

Mutations in *nfxA*, an allele of *gyrA*, increase the MIC of norfloxacin in *E. coli*. Mutations in a separate gene, nfxB, lead to decreased expression of the OmpF porin channel and to increases in the MIC of tetracycline, chloramphenicol, and cefoxitin, as well as of norfloxacin. Double mutants in *nfxA* and *nfxB* are frankly resistant to norfloxacin (Table 4) (132).

Table 4. Cross-resistance of Norfloxacin with Other Agents

Genotype	MIC (mg/l) of indicated agent for genotype Norfloxacin	Tetra-cycline	Chloram-phenicol	Cefoxtin
Wild-type	0.08	4	8	4
nfxA	0.64	4	4	8
nfxB	0.32	16	32	>32
nfxA + *nfxB*	10-20	16	>32	>32

Changes in OmpA and OmpC do not decrease susceptibility to fluoroquinolones. Although mutations affecting outer membrane permeability may decrease susceptibility to fluoroquinolones and to unrelated antimicrobials in tandem, fluoroquinolones may also inhibit strains of Enterobacteriaceae and *P. aeruginosa* that are resistant to cephalosporins, monobactams, carbapenems, and aminoglycosides on the basis of permeability mutations (132).

Quinolone resistance in *E. coli* has been associated with a mutation in the A subunit of DNA gyrase that blocks enzyme inhibition by these drugs (133).

Resistance to quinolones in *E. coli* may closely resemble that observed in *P. aeruginosa;* a single clone from a nalidixic acid-sensitive strain of *P. aeruginosa* has been shown to confer susceptibility on resistant strains of both species (134).

A strain of *E. cloacae* resistant to ciprofloxacin yielded DNA gyrase in which the A subunit conferred resistance to inhibition of the enzyme by fluoroquinolones (135).

An LPS-deficient mutant (*rfaE*) of *S. typhimurium* shows enhanced susceptibility to nalidixic acid and other lipophilic quinolones, but the mutation does not enhance susceptibility to hydrophilic fluoroquinolones. Thus LPS may present a barrier to the permeation of the bacterial outer membrane by hydrophilic quinolones (19).

Fluoroquinolone resistance in a strain of *S. marcescens* was associated with resistance of purified bacterial DNA gyrase to inhibition by these drugs (136).

DNA gyrase subunits A and B have been purified from a strain of *P. aeruginosa* resistant to nalidixic acid and fluoroquinolones. Resistance to inhibition of DNA gyrase supercoiling activity was found to be associated with subunit A of the enzyme from the mutant strain (137). Norfloxacin-resistant strains of *P. aeruginosa* selected *in vitro* included mutations in either the *gyrA* locus or in another gene, designated *nfxB.* The latter mutation was associated with diministed uptake of norfloxacin, appearance of a new 54-kilodalton outer-membrane protein, and hypersusceptibility to β-lactams and aminoglycosides (138).

Emergence of resistance to fluoroquinolones in clinical use has been reported most notably in pulmonary infections

with *P. aeruginosa* in patients with cystic fibrosis (132). Ciprofloxacin-resistant strains of *P. aeruginosa* were isolated from two of 24 cystic fibrosis patients in Salt Lake City, from one of 28 in Norfolk, and from one-third of 29 in Irvine. No correlation was observed in the latter city between clinical response to ciprofloxacin therapy and antimicrobial resistance (MIC > 2 mg/l), and ciprofloxacin resistance did not correlate with changes in bacterial protease production. Only the group in Irvine used antimicrobial-containing selective media, thus ciprofloxacin resistance may often involve only a subpopulation of a patient's *P. aeruginosa* burden. Reemergence of ciprofloxacin-susceptible strains usually occurs within six months of discontinuation of fluoroquinolone therapy (139).

Resistance to ciprofloxacin developed among bacterial isolates recovered during therapy for infection with *P. aeruginosa* in 9 (36%) of 25 patients treated with ciprofloxacin alone and in 2 (18%) of 11 patients treated with ciprofloxacin plus an aminoglycoside or antipseudomonal penicillin. Resistant bacteria included *P. aeruginosa* (9 strains), *S. aureus* (4 strains), *S. epidermidis* (2 strains), and one strain apiece of *E. coli* and *S. marcescens.* Decreased susceptibility was associated with persistence of nine isolates and with clinical failure in six patients (140).

There is increasing recognition that *P. cepacia,* like *P. aeruginosa,* is an important respiratory pathogen in patients with cystic fibrosis. Although *P. cepacia* is often susceptible to ciprofloxacin, resistance to this drug has been documented. Burns and colleagues studied a strain of *P. cepacia* that had been isolated from a patient with cystic fibrosis and was resistant to chloramphenicol, ciprofloxacin, and trimethoprim, apparently on the basis of poor drug permeability. Cloning of whole-cell DNA indicated that the genes for resistance to the three drugs were linked within a 26-kilobase cluster (141).

Other examples of the development of resistance to fluoroquinolones during therapy include wound infections with *S. marcescens* or *S. aureus* and urinary-tract infections with *E. coli* or *P. aeruginosa,* particularly in the setting of poor blood supply or indwelling bladder catheters. Development of resistance to fluoroquinolones has not necessarily implied clinical failure. Whether administration of other antimicrobials concomitantly with fluoroquinolones will prevent the development of resistance to the latter drugs is not established (132).

Experimental Models

Cells of *E. coli, P. aeruginosa,* and *S. aureus* that are harvested from an overnight subculture in drug-free medium after previous incubation for 24 h at a subinhibitory concentration of ciprofloxacin show enhanced killing *in vitro* by human leukocytes (142).

S. aureus exposed *in vitro* to enoxacin in a two-compartment model shows initial killing but subsequent regrowth after 6 h. Addition of human leukocytes to the system forestalls bacterial regrowth only when the white cells are added 6 h after introduction of the drug (143).

Subinhibitory levels of pefloxacin enhance phagocytosis of *E. coli* and reduce adherence of uropathogenic strains to human uroepithelial cells (144). Enoxacin, at concentrations below the MIC, reduces adherence of uropathogenic *E. coli* to uroepithelial cells and detaches previously adherent organisms. Electron microscopy reveals that exposure to enoxacin at subinhibitory levels causes abnormalities in bacterial cell structure, including elongation of the organisms and reduction in or loss of cell fimbriae, which mediate adhesion to host cells (145).

Fluoroquinolones have appeared to equal conventional antimicrobial regimens in the therapy of experimental animal infections, including *S. aureus* endocarditis and osteomyelitis; *P. aeruginosa* meningitis, pneumonia, endocarditis, and peritonitis; and *E. coli* meningitis. In experimental osteomyelitis due to *P. aeruginosa,* ciprofloxacin appears superior to tobramycin plus ticarcillin, but in some animals ciprofloxacin-resistant strains emerge during therapy (146).

Ciprofloxacin is more active than gentamicin or cefotaxime against stationary-phase *E. coli in vitro* and in the murine granuloma pouch model (147). Ciprofloxacin is also superior to ceftriaxone in the treatment of experimentally induced *E. coli* arthritis in rabbits (148). Ciprofloxacin shows additive activity with tobramyin and synergy with azlocillin or ceftazidime when used in experimental *P. aeruginosa* infections in mice rendered neutropenic with cyclophosphamide (149).

In combination with clindamycin or metronidazole, both ciprofloxacin and pefloxacin are effective against experimentally induced peritonitis in rats (150).

Fluoroquinolones are active in experimental models of pyelonephritis (151) and pleural empyema (152).

Difloxacin has activity in experimental models of intacellular infection with *S. typhimurium* (153, 154), *L. pneumophila* (Fernandes), and *S. aureus* (Easmon).

Therapeutic Applications

> What is art
> But life upon the larger scale, the higher,
> When, graduating up in a spiral line
> Of still expanding and ascending gyres,
> It pushes toward the intense significance
> Of all things, hungry for the Infinite?
> E. B. Browning, *Aurora Leigh*

Fluoroquinolones are highly effective in treatment of uncomplicated urinary-tract infections, but data on single-dose therapy are few, and there is evidence of treament failures in infections with *S. saprophyticus.* Fluoroquinolones also appear to be effective in treating complicated infections of the urinary tract, but more data are needed on long-term follow-up cultures. The fluoroquinolones provide the unprecedented ability to treat urinary-tract infections caused by *P. aeruginosa* with an oral agent, but therapeutic failures and emergence of resistant strains during therapy are not uncommon. Fluoroquinolones may be effective in prostatitis, but further studies are needed in this area, too. Evaluation of the role of fluoroquinolones in the treatment of urinary-tract infections in patients with renal failure awaits studies in affected populations (155). Urinary-tract infections should be treated with one or two doses of 500 mg ciprofloxacin or norfloxacin po (32).

Gasser and colleagues reported that a seven-day course of ciprofloxacin was effective in 85% of patients with complicated urinary-tract infections, as judged by urine cultures obtained five to nine days after conclusion of therapy. Increasing the dose from 250 mg po bid to 500 mg or 750 mg bid increased neither the efficacy nore the attack rate of adverse reactions, which was 11% overall (156). In one study from Mexico, ciprofloxacin appeared to be superior to trimethoprim plus sulfamethoxazole in the treatment of urinary-tract infections (157).

Ciprofloxacin levels in stool range as high as 2200 mg/l after oral administration of 500 mg bid. There is

marked diminution of Enterobacteriaceae, streptococci, and staphylococci. Anaerobic bacteria are less affected and acquire resistance to the drug. Increase in concentrations of *E. faecium* has also been reported. Replacement of indigenous microflora by inherently resistant microorganisms has generally not been a problem, although Dutch workers have noted an increase in fecal concentrations of *Candida albicans* (158). Return of the normal flora occurs within two weeks of discontinuting ciprofloxacin (159). Investigators at the University of Naples report that ciprofloxacin, 250 mg po bid, decreased blood ammonia levels, endotoxin titers, and fecal concentration of Enterobacteriaceae, with improvement in clinical status in five of six patients with cirrhosis and hepatic encephalopathy (160).

Although superior to trimethoprim plus sulfamethoxazole in eradicating enteric pathogens from the stools of patients with traveler's diarrhea, ciprofloxacin has not been shown to equal the antifolate combination in clinical efficacy in one study population in Guadalajara. This group has a low prevalence rate of *C. jejuni,* however, against which ciprofloxacin has superior activity *in vitro* (71).

Salivary flora is little affected by ciprofloxacin except for a reduction in *Neisseria* spp. (159). The potential of ciprofloxacin as an agent for the treatment of community-acquired pneumonia is limited by marginal activity of the drug against *S. pneumoniae* (38), but good results have been reported in the treatment of patients with severe respiratory-tract infections in an uncontrolled study from Italy (161). Clinical trials of the treatment of acute exacerbations of chronic bronchitis, pneumonia, and pulmonary infection in cystic fibrosis have resulted in clinical and bacteriologic failures most frequently in cases of infection with the pneumococcus and with *P. aeruginosa* (38). Addition of ciprofloxacin to erythromycin and rifampin has been stated to improve the outcome in patients with severe Legionnaires' disease in comparison with that of historical controls (162).

Several groups have reported success in the treatment of bone and joint infections with ciprofloxacin, although emergence of resistant *P. aeruginosa* or *S. aureus* or persistence of *P. aeruginosa* have not been uncommon (59). Investigators in Verona found that ciprofloxacin, 500 mg po bid for up to 75 days, was effective in four cases apiece of acute and chronic osteomyelitis due to *S. aureus* (163).

Tice, Marsh, and Craven treated 15 patients with osteomyelitis with ciprofloxacin, 750 mg po bid, for an average of eight weeks; five were considered cured and another seven improved. Relapse (in two patients) and failure (in one) were associated with persisting open wounds and with infection with *P. aeruginosa* (164). After initial intravenous courses of 200 mg q12h in some patients, ciprofloxacin, 750 mg po bid, was effective in 15 of 19 cases of chronic osteomyelitis in exacerbation caused by gram-negative bacilli, including infections with *E. cloacae* and *S. enteritidis,* and 13 of 17 case of *P. aeruginosa* infection (165).

Seventeen of 23 patients with acute (7 cases) or chronic (16 patients) gram-negative or polymicrobial osteomyelitis were deemed clinically cured after therapy with ciprofloxacin, 750 mg po q12h, for up to 23 weeks. All six cases with recurrent disease after cessation of therapy responded to reinstitution of ciprofloxacin or surgery (166).

Ciprofloxacin is as effective as trimethoprim plus sulfamethoxazole plus colistin in prevention of infection in leukemic and neutropenic patients. In two small series, ciprofloxacin plus netilmicin or ciprofloxacin plus benzylpenicillin were at least as good as piperacillin plus netilmicin in the treatment of bacterial infection in neutropenic and other compromised hosts (97).

Ciprofloxacin doses for moderate to severe systemic infections might range from 500 mg po q12h to 750 mg po q8h (32). Among 488 patients with bacterial infections treated with ciprofloxacin in Frankfurt am Main, relapse, resistance, or reinfection was most common in urinary-tract infections caused by *Klebsiella* spp. (10 of 32 cases) or *P. aeruginosa* (25 of 102 cases) and in respiratory-tract infections caused by *P. aeruginosa* (167).

Eron and colleagues reported that ciprofloxacin, 750 mg po bid, gave "a satisfactory response" in 44 (77%) of 55 patients with infections with *P. aeruginosa* treated in their Virginia practice. Bacteria persisted in 12 (21%) of the 57 infections, with clinical failure in five of these 12 (168). In one series of patients at a Connecticut hospital treated with ciprofloxacin for serious pseudomonal infections, 14 (87.5%) of 16 responded clnically, but only 7 (47%) of 15 responded bacteriologically. Failures were seen in patients with chronic pulmonary disease or persistent soft-tissue foci (169). Swiss investigators have reported clinical and bacteriologic success in 17 (85%) of 20 infections with *P.*

aeruginosa outside the lung but in only two of six cases of pulmonary disease (170).

Improvement has been reported in a small series of patients from Seattle with severe pulmonary disease due to cystic fibrosis who were treated with ciprofloxacin. Increased exercise tolerance and appetite and decreased concentrations of *Pseudomonas* were also seen in cystic fibrosis patients in Salt Lake City treated with ciprofloxacin; the clnical response was comparable to that seen in a comparison group of patients receiving tobramycin plus azlocillin (139).

Most of 29 cystic fibrosis patients in Irvine considered to have impending exacerbation of pulmonary disease on the basis of decreasing excercise tolerance and increasing sputum production had major (52%) or minor (38%) clinical improvement on ciprofloxacin, 750-1000 mg twice daily. Improvement in pulmonary function testing and bacterial counts, however, was not sustained after discontinuation of a two-week regimen (139). In one series from Quebec, ciprofloxacin therapy lead to an increase in the MIC of that drug in strains of *P. aeruginosa* isolated from the sputum of patients with cystic fibrosis (39).

In patients with cystic fibrosis an initial dose of 15 mg/kg/day has been suggested, with a gradual increase to 25-30 mg/kg/day to give peak serum concentrations of 3-4 mg/l (139).

Ciprofloxacin is comparable to cefotaxime in the treatment of infections of the skin and soft tissues (171). There is little experience with the treatment of acute and chronic sinusitis and of acute otitis media with ciprofloxacin. This drug was reported to be effective in eight of 12 patients with chronic otitis media caused by *P. aeruginosa* reported in three small series (36). Seven of 12 adult Greeks with chronic otitis media, acute otitis, externa, or malignant otitits externa were cured by ciprofloxacin therapy lasting from two to 16 weeks. Concomitant surgery was required in four patients (172). Ciprofloxacin, with aspiration, debridement, and surgery as indicated, was effective in 39 (66%) of 59 patients seen in a European cooperative study who had chronic suppurative otitis. Bacteriologic failures were most common in infections with *P. aeruginosa* (14 of 24 strains eradicated) and *S. aureus* (five of 12 eradicated) (173).

Ciprofloxacin with or without tobramycin was effective in treatment of two refractory cases of ventriculitis or meningitis caused by *P. aeruginosa.* Ciprofloxacin was also effective in suppression of relapsing *P. aeruginosa* meningitis in another patient (43).

Italian investigators report an 80% success rate in the treatment of complicated urinary-tract infections with norfloxacin (174). Norfloxacin was found to be effective in simple and complicated urinary-tract infections and in postcatheter bacteriuria in a study from Spain (175). In one study from the United Kingdom, nofloxacin was superior to trimethoprim in the treatment of urinary-tract infections in the elderly, but recurrent episodes were frequent in the quinolone-treated group (176). A multicenter study reported by the manufacturer involved the administration of norfloxacin, 400 mg po bid, for six to 12 weeks to 123 patients with chronic urinary-tract infections. Of 91 evaluable patients, 73 (80%) "had bacteriologic evidence of eradication" of the infections three to six weeks after termination of therapy (177).

Norfloxacin, 200 mg po qd, is superior to placebo as prophylaxis in women who have had at least three episodes of uncomplicated urinary-tract infections caused by a facultative organism over the previous year (178).

Oral norfloxacin reduces concentration of *Branhamella* in saliva and of Enterobacteriaceae in feces, with varying effects on staphylococci and streptococci, but otherwise has little effect on normal oral and intestinal microflora (150, 179). Norfloxacin, 800 mg po two hours before surgery, is as effective as intravenous piperacillin in prophylaxis of patients undergoing biliary tract surgery (180). This fluoroquinolone is at least as efficacious as ampicillin in the therapy of shigellosis, including disease caused by ampicillin-susceptible strains, and at least as effective as nalidixic acid against Shiga dysentery (71). The drug was considered to be "effective and safe for the treatment of acute bacterial gastroenteritis" on the basis of an uncontrolled study with 37 evaluable cases in Thailand (181).

Norfloxacin is superior to placebo in the prevention of infection in leukemic and neutropenic patients (97).

Desplaces and Acar in Paris reported apparent cures in 17 (85%) if 20 patients with bone and joint infections due to *S. aureus,*, including 11 with total joint arthroplasty or

internal fixation hardware, after a mean of six months' therapy with pefloxacin, but three patients developed pefloxacin-resistant strains. Of 14 subsequent patients with *S. aureus* infections of bone and joints treated with a combination of pefloxacin and rifampin, all have apparently been cured. Four of the six apparent cures of *S. aureus* injections of total joint arthroplasty did not require surgery (59).

Eighteen patients with polymicrobial or gram-negative infections of bone and joints, including nine with total joint arthroplasty or internal fixation, were treated with pefloxacin for a mean of six months plus an initial three-week course of an aminoglycoside or a β-lactam antibiotic. One patient developed erythroderma necessitating discontinuation of therapy and one had had persistent infection with *E. faecalis;* the other 16 patients were apparently cured. Two of five successfully treated patients with total joint arthroplasty did not require surgery. Nine cases were treated successfully with internal fixation devices in place. Pefloxacin has also been used successfully in bone and joint infection by other investigators (59, 182).

Twenty-one (72%) of 29 episodes of fever in patients with <500 granulocytes/'1 were successfully treated with pefloxacin monotherapy (183).

The effects of pefloxacin and ofloxacin on the intestinal microflora appear similar to those of the other fluoroquinolones (150).

Ofloxacin is effective in the therapy of urinary-tract infections, including acute prostatitis and acute exacerbations of acute prostatitis (184, 185). Ofloxacin is reported to be at least as effective at trimethoprim plus sulfamethoxazole in the treatment of complicated urinary-tract infections (186) and in those occurring in patients with renal allografts (187).

Ofloxacin is reportedly efficacious in the treatment of enterocolitis and enteric fever due to *S. typhi* and nontyphoid *Salmonella* spp. as well as in a single typhoid carrier with cholelithiasis (188).

Ofloxacin is comparable to cephalexin in the treatment of outpatients with infections of the skin and soft tissues (189) and is also effective in therapy of skeletal infections (182, 185, 190). However, of three cases of

chronic otitis media, one of malignant otitis externa, and two of uncomplicated otitis externa reported from Athens, only one of the cases of uncomplicated otitis externa was cured by treatment with this drug. Furthermore, resistance to ofloxacin developed during therapy in isolates of *P. aeruginosa* from the case of malignant otitis externa and from one of the three with chronic otitis (191). Ofloxacin is reportedly superior to amoxicillin in the treatment of "infective episodes of bronchiectasis" caused by gram-negative bacilli (192) and this quinolone was considered to be effective in lower respiratory-tract infections in an uncontrolled study from Italy (193). Oral ciprofloxacin, 750 mg bid, is comparable to intravenous tobramycin plus azlocillin in the treatment of acute pulmonary deterioration caused by *P. aeruginosa* in patients over age 18 with cystic fibrosis (194).

Single-dose treatment with ofloxacin is effective therapy for gonorrhea, including cases caused by penicillinase-producing *N. gonorrhoeae* (PPNG) (195, 196). Ofloxacin is also reportedly effective in treatment of first episodes of salpingitis and endometritis attributed to a variety of pathogens, including *C. trachomatis* (197).

Enoxacin is superior to placebo in prophylaxis against urinary-tract infections in patients undergoing prostatectomy (198). Eighteen (72%) of 25 urology patients with complicated urinary-tract infections were cured after treatment with enoxacin, 200 mg po bid, for six to 14 days (75). This drug is also effective in the treatment of urinary-tract infections in spinal injury patients, but relapses, reinfections, and superinfections are common sequelae, and infections with *E. faecalis* do not respond (199). Enoxacin is better than amoxicillin for the treatment of chronic suppurative otitis media (200). This drug offers no advantage over trimethoprim plus sulfamethoxazole in the therapy of infections of the lower respiratory tract, even in patients in whom respiratory secretions are negative for pneumococcal antigen (201).

Adverse Effects

> But--alack!--I am undone, for I have No
> More Twist--
> Beatrix Potter, *The Tailor of Gloucester*

A history of hypersensitivity to quinolones is a contraindication to the administration of fluoroquinolones.

These drugs should also not be prescribed for children or adolescents or to pregnant or lactating females and should be administered with caution, if at all, to patients with underlying disease of the central nervous system (202).

Reports on adverse reactions (Table 5) and abnormal laboratory findings (Table 6) associated with the administration of fluoroquinolones have been summarized by Halkin (203).

Table 5. Pooled attack rates of major signs and symptoms of adverse reactions to the fluoroquinolones.

Body system, signs or symptoms	No. of patients with sign or symptom/1,000 treated with indicated agent*			
	Ciprofloxacin	Ofloxacin	Norfloxacin	Pefloxacin
Gastrointestinal				
Nausea, vomiting	23.3 (4.7)	9.0 (3.5)	1.1	35.6 (4.2)
Pain	2.9 (0.0)	9.1 (2.0)	6.9	12.7 (3.4)
Diarrhea	14.8 (0.6)	4.3 (1.1)	0.8	3.4 (0.8)
CNS				
Dizziness	5.4 (1.2)	1.7 (0.7)	5.2	2.5 (0.0)
Headache	3.0 (0.0)	1.4 (0.6)	3.4	0.8 (0.0)
Insomnia	0.0 (0.0)	3.4 (1.2)	1.7	2.5 (0.0)
Skin				
Rash	8.3 (0.0)	2.8 (2.6)	4.3	12.7 (7.6)
Pruritis	4.7 (0.0)	0.6 (0.4)	1.7	0.0 (0.0)
Photosensitivity	0.0 (0.0)	†	0.0	9.3 (2.5)
Edema	1.2 (0.0)	0.4 (0.0)	0.0	0.0 (0.0)

NOTE. Detailed data for ciprofloxacin are from the United States and Europe; and for ofloxacin, from phase III and phase IV studies in Germany. For norfloxacin, detailed data were not available.

* Numbers in parentheses are the number of patients/1,000 treated who had a severe reaction that necessitated discontinuation of therapy with agent.

† Three cases of photosensitivity were reported from Switzerland among 21 patients with cystic fibrosis

Table 6. Attack rates of altered laboratory findings due to the fluoroquinolones.

Laboratory finding	No. with finding/ 1,000 treated with indicated agent		
	Ciprofloxacin	Ofloxacin	Pefloxacin
Leukopenia	0.0	5.0	2.5
Decrease in hemoglobin/hematocrit	0.0	1.9	5.9
Thrombocytosis	0.6	3.5	5.9
Eosinophilia	2.4	5.0–19.3*	2.5
Elevated liver enzymes†	24.9‡	24.0	17.8§
Decreased renal function‖	1.8	13.1	1.8
Overall	61.0	76.0	45.0

* Only one of 92 cases of eosinophilia was associated with skin rash.

† Elevated levels of serum aspartate aminotransferase, serum alanine aminotransferase, or alkaline phosphatase.

‡ All three patients whose elevations in hepatic enzymes necessitated discontinuation of therapy had histories of viral hepatitis.

§ Eleven of 21 patients with greater than threefold elevations in hepatic enzymes were severely ill, receiving ventilatory support, recovering from surgery or trauma, or receiving multiple drugs other than pefloxacin.

‖ Elevated levels of blood urea nitrogen and creatinine and decreased creatinine clearance.

Nausea, vomiting, and diarrhea are frequent in patients receiving 4-quinolones (202). Common side-effects seen in a large group of patients treated with ciprofloxacin in Germany included diarrhea, usually mild, nausea, and dizziness (167). Eron and colleagues reported gastrointestinal side-effects in 21% of their patients treated with ciprofloxacin, with the highest attack rate in small elderly patients (168). Pseudomembranous enterocolitis was reported in at least one of 34 patients treated with pefloxacin in one series (204).

Elevations of serum bilirubin and aminotransferase levels may occur in patients receiving fluoroquinolones (202).

In immature animals fluoroquinolones cause damage to diarthrodial joint cartilage (202, 205). Such reactions have also been reported with nalidixic acid in experimental animals but not in children receiving that drug. However patients receiving fluoroquinolones have developed arthralgias and myalgias (202).

Mild arthralgia occurred in two of 23 patients treated with pefloxacin in two Paris hospitals (206). Joint pain was reported by a patient with cystic fibrosis in whom the concentration of ciprofloxacin in serum exceeded 4 mg/l (139). Three girls aged 10-16 years with cystic fibrosis in

the United Kingdom were reported to have arthralgias or arthritis of the knees and other joints that resolved upon discontinuation of ciprofloxacin. Radiographic studies in one of the patients were normal (207).

Interstitial nephritis, microscopic hematuria, and azotemia have been reported in dogs and other animals given fluoroquinolones in doses sufficient to cause crystalluria. The risk of nephropathy appears to be increased in experimental animals by high-dose quinolone administration and alkaline urine. Azotemia, crystalluria, cylindruria, and hematuria have been reported in man (202).

Five of six patients with cystic fibrosis treated with ciprofloxacin developed sterile pyuria, leukocyte casts, and azotemia. Evidence of the development of interstitial nephritis was felt to correlate with a history of penicillin allergy (139). Acute renal failure with allergic interstitial nephritis documented by biopsy occurred in a patient receiving ciprofloxacin after initial therapy for *S. aureus* pneumonia treated with cefazolin, gentamicin, and metronidazole (208).

Fluoroquinolones can cause CNS disturbances in man, including anxiety, depression, euphoria, somnolence, insomnia, and seizures. Other reported associations include headache, dizziness, light-headedness, confusion, hallucinations, agitation, nightmares, and mania. Some patients receiving these drugs develop diplopia, altered color vision, eye pain, tinnitus, or diminution in taste or smell. Fluoroquinolones may interact with CNS GABA receptors (202).

In one German study, 20% of vounteers taking ciprofloxacin, 200-400 mg po, developed headache (209). Three instructive cases of transient confusion, hallucinations, or depression in patients receiving ciprofloxacin or pefloxacin have been reported from Israel (210).

A single convulsion occurred in a woman with apparently normal renal function who was receiving norfloxacin, 400 mg twice daily, but hyponatremia, alkalosis, and withdrawal of thiothixene may have contributed to the seizure (211). Coadministration of fenbufen with fluoroquinolones may be epileptogenic (202).

Cutaneous reactions are not rare. Quinolones, particularly nalidixic acid and pefloxacin, have produced photosensitivity reactions (202).

The 4-quinolones can produce hypersensitivity reactions (202). A case of severe rash with laryngeal edema thought to be related to the administration of ciprofloxacin has been reported by Mexican workers (171). Erythroderma with "multiple organ failure" developed in one of 26 compromised hosts treated with pefloxacin monotherapy for a variety of bacterial infections (212).

Transient rises in serum triglycerides were observed in two of 23 patients treated with prolonged courses of ciprofloxacin for osteomyelitis (166).

Cataracts and azoospermia and testicular damage have been observed in animals after treatment for months with high doses of fluoroquinolones (202). Bolus administration of fluoroquinolones causes hypotension in anesthetized cats and dogs (202).

One of seven volunteers receiving 400 mg enoxacin iv in a one-hour infusion developed periorbital edema, and another volunteer experienced marked sneezing. Symptoms in both persons subsided with discontinuation of the infusion (32).

Adverse reactions were observed in 32% of patients treated with ofloxacin in a collaborative series from Seattle and Charleston, but most of these reactions were mild and were not judged to be probably drug-related (189).

Concurrent ciprofloxacin administration raises serum levels of theophylline, although the magnitude of the elevation of the concentration of the xanthine does not correlate with the peak level of the quinolone (48, 26, 139). Fluoroquinolones can also interfere with the metabolism of caffeine (202).

Inhibition of eukaryotic type II topoisomerases is not thought to occur at concentrations of quinolone antimicrobials achieved in serum (13). The quinolones also do not appear to be mutagenic (202, 231)

Conclusions

> "I take it that you haven't come to any decision yet on my suggestions. That's right. In fact, I should have advised you against it had you attempted an immediate decision. It's like splitting hairs to distinguish the advantages and disadvantages. You must weight everything very carefully. On the other hand you mustn't lose too much time either."
>
> Franz Kafka, *The Trial*

Indications for the use of fluoroquinolones include chronic osteomyelitis, acute exacerbations of cystic fibrosis, urinary tract infections, bacterial and chlamydial prostatitis, bacterial enteritis, and severe nosocomial infection with gram-negative bacilli. Other potential uses include reduction of gut flora and treatment of chronic bacterial infections and of traveler's diarrhea (69).

The Medical Letter deems ciprofloxacin "an economical alternative to parenteral therapy for many serious infections, including infectious diarrhea, osteomyelitis, and respiratory infections in patients with cystic fibrosis" (214).

A symposium held in March 1987 on the issue of ciprofloxacin in patients with cystic fibrosis concluded, "Ciprofloxacin may be useful as an alternative to parenteral therapy for cystic fibrosis patients older than 18 years of age with exacerbations of bronchopulmonary infection. There are not data to support its efficacy and safety in patients younger than 18 years of age; hence its administration to patients in this age group remains investigational. Until more information is abvailable the usefulness of this agent will be for patients whose sputum contains ciprofloxacin-susceptible *P. aeruginosa*." It was suggested that the duration of therapy be limited to two to four weeks for any single course. The need to avoid neglecting ancillary measures (chest physiotherapy, postural drainage, nutrition, hydration, and psychologic support) was emphasized. Ciprofloxacin use in patients younger than 18 years or for chronic suppressive therapy in adults "is still investigational" (139).

According to The Medical Letter, since most urinary tract pathogens "are also susceptible to many other antibacterial agents,...older, less expensive drugs are preferred" to norfloxacin, which, however, "should prove useful for oral therapy of complicated urinary tract infections caused by multiple-antibiotic-resistant *Enterobacteriaceae, Pseudomonas aeruginosa,* or enterococci (215).

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