35 Quinolones

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SHORT VIEW SUMMARY

- Usual adult dose
  - Norfloxacin: oral (PO) 400 mg every 12 hours
  - Ciprofloxacin: PO 250 to 750 mg every 12 hours; intravenous (IV) 200 to 400 mg every 12 hours
  - Ofloxacin: PO or IV 200 to 400 mg every 12 hours
  - Levofloxacin: PO or IV 250 to 750 mg daily; 240-mg nebulizer solution (available outside United States)
  - Moxifloxacin: PO or IV 400 mg daily
  - Gemifloxacin: PO 320 mg daily
  - Delafloxacin: PO 450 mg every 12 hours; IV 300 mg every 12 hours
- Renal and hepatic failure: decrease dose in renal failure for all except moxifloxacin.
- Cerebrospinal fluid penetration: low
- Adverse effects
  - Common: gastrointestinal upset, central nervous system stimulation
  - Less common: seizures, tendinitis and tendon rupture, *Clostridioides difficile* (formerly *Clostridium difficile*) disease, dysglycemia, exacerbations of myasthenia gravis, peripheral neuropathy
- Contraindications: prior quinolone allergy, prior neuropathy
- Drug-drug interactions
  - Do not take oral formulations with aluminum-, calcium-, magnesium-, or iron-containing compounds.
  - Avoid other agents that prolong the QT interval (particularly with moxifloxacin).
  - Avoid concomitant use of tizanidine.
  - Variable interactions occur with warfarin; monitor international normalized ratio.
- Indications (US Food and Drug Administration approved)
  - Norfloxacin: used to treat uncomplicated and complicated urinary tract infections and prostatitis. Can be used for urethral or cervical gonorrhea *only* if infecting isolates are known to be susceptible.
  - Ciprofloxacin: used to treat complicated and uncomplicated urinary tract infections, chronic bacterial prostatitis, uncomplicated cervical and urethral gonorrhea (*only* if infecting isolates are known to be susceptible), complicated intraabdominal infections, bacterial diarrhea, typhoid fever, acute bacterial sinusitis, lower respiratory tract infections (when *not* caused by *Streptococcus pneumoniae*), inhalational anthrax, skin and skin structure infections, and bone and joint infections.
  - Ofloxacin: used to treat complicated and uncomplicated urinary tract infections, bacterial prostatitis, uncomplicated cervical and urethral gonorrhea (*only* if infecting isolates are known to be susceptible), nongonococcal urethritis and cervicitis caused by *Chlamydia trachomatis,* acute pelvic inflammatory disease, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, and uncomplicated skin and skin structure infections.
  - Levofloxacin: used to treat complicated and uncomplicated urinary tract infections, acute pyelonephritis, chronic bacterial prostatitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, hospital-acquired pneumonia, inhalational anthrax, acute bacterial sinusitis, and complicated and uncomplicated skin and skin structure infections. Nebulizer solution used to treat chronic pulmonary infections due to *Pseudomonas aeruginosa* infections in patients with cystic fibrosis (outside United States).
  - Moxifloxacin: used to treat community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, and alternative agent in multidrug-resistant tuberculosis (off-label use).
  - Gemifloxacin: used to treat community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis.
  - Delafloxacin: used to treat acute bacterial skin and skin structure infections.

The first member of the quinolone class of antimicrobial agents, nalidixic acid, is a 1,8-naphthyridine structure that was identified by Lesher and associates in 1962 as a byproduct of chloroquine synthesis. Oxolinic acid and cinoxacin were also developed in the 1970s, but it was the identification in the 1980s of the fluorine- and piperazinyl-substituted derivatives with substantially greater potency and expanded spectrum that enabled expansion of this class of compounds. A broad spectrum of activity, good oral absorption, and generally good overall tolerability have resulted in extensive clinical use of the newer fluoroquinolones. Several quinolones, however, including temafloxacin, sparfloxacin, grepafloxacin, trovafloxacin, and gatifloxacin, were removed from clinical use after approval because of toxicities, which were uncommon but severe in some cases. This chapter focuses on those quinolones that are currently in clinical use.

CHEMICAL STRUCTURES

All current quinolone derivatives in clinical use have a dual ring structure with a nitrogen at position 1, a carbonyl group at position 4, and a carboxyl group attached to the carbon at the 3 position of the first ring (Fig. 35.1). Several different dual ring structures—cinnoline (nitrogens at positions 1 and 2), pyridopyrimidine (nitrogens at positions 1, 6, and 8), and 2-pyridone (a dual ring structure with the nitrogen located at the junction of the two rings)—have been developed, but quinolones, which themselves have a carbon at position 8 in the second ring, and naphthyridines, which contain a nitrogen at position 8, have been most widely successful. Both quinolones and naphthyridines, however, are commonly referred to as quinolones.

Nalidixic acid is a 1,8-naphthyridine with 1-ethyl and 7-methyl substituents (see Fig. 35.1). Oxolinic acid (quinolone ring; see Fig. 35.1) and cinoxacin (cinnoline ring; not shown in Fig. 35.1) also have 1-ethyl substitutions, as well as a dioxolo ring bridging positions 6 and 7. Potency is greatly improved by the addition of a fluorine at position 6, and potency against gram-negative bacteria is further enhanced by the addition of a piperazinyl (norfloxacin, enoxacin, ciprofloxacin), methyl-piperazinyl (pefloxacin, ofloxacin, lomefloxacin, fleroxacin, temafloxacin, levofloxacin, grepafloxacin, gatifloxacin), or dimethyl-piperazinyl (sparfloxacin) substituent at position 7.[1] Methyl substituents on the piperazine ring generally result in improved oral bioavailability. These structural features are common to most of the newer quinolone derivatives now in clinical use. Pyrrolidinyl (tosufloxacin, clinafloxacin, gemifloxacin) or dual ring substituents (trovafloxacin, moxifloxacin, sitafloxacin) at position 7 enhance activity against gram-positive bacteria. Delafloxacin

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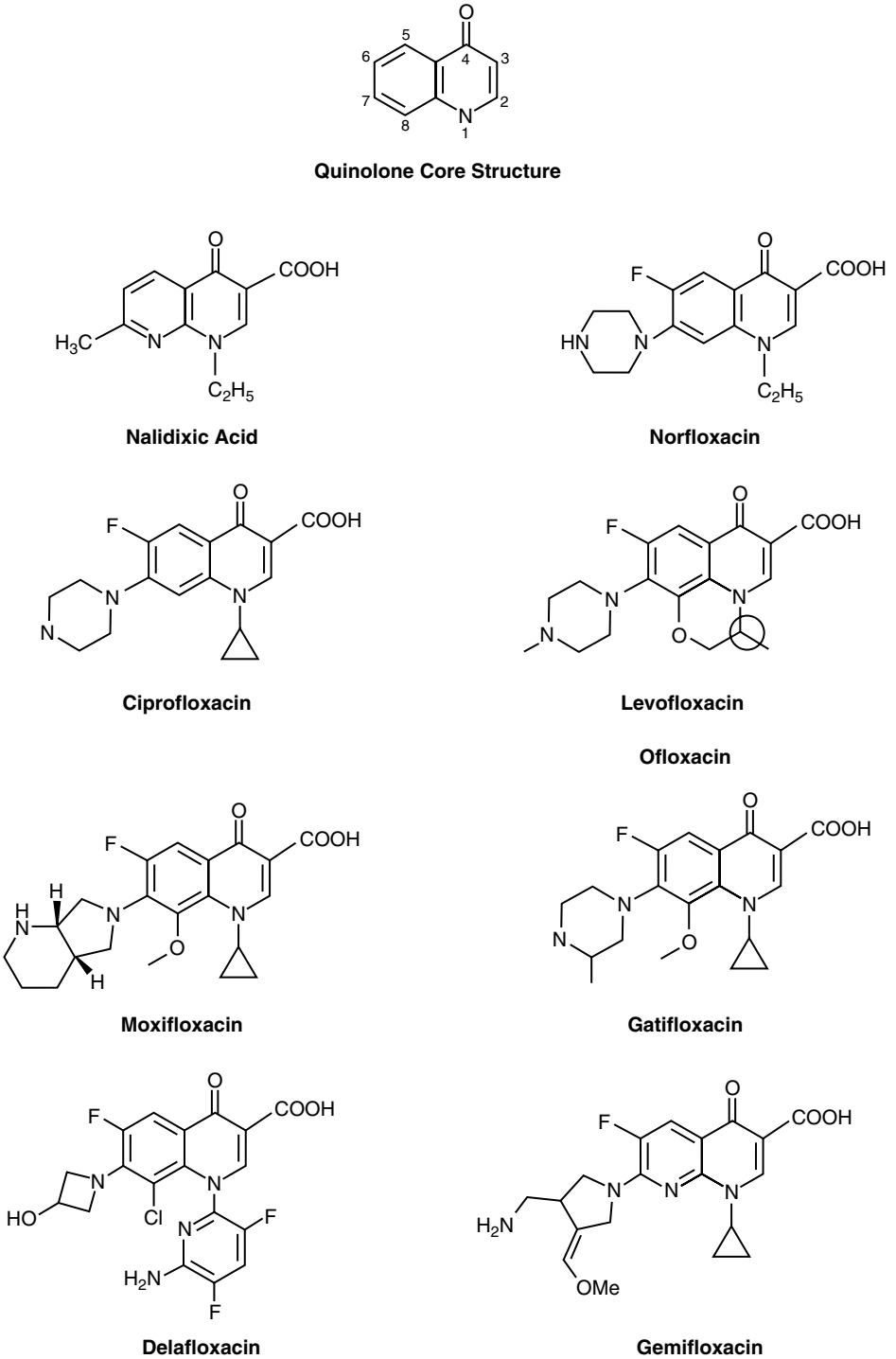

FIG. 35.1 Structures of selected quinolones in clinical use or under development. The circle in the levofloxacin structure indicates the asymmetric carbon resulting in the stereoisomers that make up the racemic mixture in ofloxacin. Levofloxacin is the more active of the two stereoisomers (levofloxacin and ciprofloxacin) of ofloxacin.

is distinct because of its anionic 3-hydroxy-1-azetidinyl substituent at position 7, which contributes to its increased potency against gram-positive bacteria and increased activity at low pH. A number of compounds (sparfloxacin, gatifloxacin, moxifloxacin, gemifloxacin) use the 1-cyclopropyl group, which enhances potency, particularly against gram-negative bacteria, and was originally identified for ciprofloxacin. The 1-difluorophenyl group found in temafloxacin, tosufloxacin, and trovafloxacin and the 1-6-amino-3,5-difluoro-2-pyridinyl found in delafloxacin add potency against gram-positive bacteria. An additional ring structure bridging positions 1 and 8 is found in ofloxacin and levofloxacin; the additional ring of ofloxacin contains an asymmetric carbon, resulting in stereoisomeric forms. Ofloxacin is a racemic mixture of the two stereoisomers, and levofloxacin is the more potent of the two and predictably is twice as potent as ofloxacin in vitro. At position 5, replacement of the hydrogen by an amino group (sparfloxacin) or a methyl group (grepafloxacin) results in some enhancement of activity against gram-positive bacteria. At position 8, addition of a halide (chlorine-clinafloxacin, fluorine-sparfloxacin, and sitafloxacin) or a methoxy group (gatifloxacin, moxifloxacin) enhances activity against anaerobic bacteria. Halides at position 8 increase the risk of phototoxicity, but methoxy groups at this position reduce risks of phototoxicity, even relative to compounds with a hydrogen at position 8.

Coming full circle in structural modifications, "desfluoro" quinolones (garenoxacin) have been identified with excellent and similar potency

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to their fluorinated counterparts but with possible reductions in joint toxicities.[2–4]

MECHANISM OF ACTION

The quinolones rapidly inhibit bacterial DNA synthesis, an event that is followed by rapid bacterial cell death. The molecular events that underlie these actions are understood in part, but details remain to be defined.[5]

Quinolones inhibit the enzymatic activities of two members of the topoisomerase class of enzymes—DNA gyrase and topoisomerase IV—and promote the cleavage of DNA in these enzyme-DNA complexes. DNA gyrase, which was the first-recognized target of quinolones, is an essential bacterial enzyme composed of two A and two B subunits, products of the *gyrA* and *gyrB* genes, respectively.[6,7] DNA gyrase uniquely catalyzes the introduction of negative superhelical twists into closed covalently circular chromosomal and plasmid DNA within the bacterial cell. The superhelical state of intracellular DNA is regulated by the actions of DNA gyrase and topoisomerase I, which removes DNA superhelical twists but is not inhibited by quinolones. DNA superhelicity affects the initiation of DNA replication and transcription of many genes. DNA gyrase is also responsible for removing positive superhelical twists that accumulate ahead of the DNA replication fork. These activities result from the enzyme's coordinated breaking of both strands of duplex DNA, passage of another segment of DNA through the break, and resealing of the break, a mechanism that defines type II topoisomerases.

Quinolones also inhibit the activities of topoisomerase IV, another type II topoisomerase that is composed of two subunits encoded by the *parC* and *parE* genes. Topoisomerase IV and DNA gyrase are structurally related; *parC* is homologous to *gyrA*, and *parE* is homologous to *gyrB*.[8] Topoisomerase IV functions to resolve (decatenate) interlinked (catenated) daughter DNA molecules that result from replication of circular DNA, to allow their segregation into daughter cells. Thus DNA gyrase and topoisomerase IV have distinct essential roles in bacterial DNA replication.[9] Gyrase can mediate the functions of topoisomerase IV (albeit less efficiently as a decatenase), but topoisomerase IV is unable to introduce negative supercoils into DNA, a function that is unique to DNA gyrase. A few species of human pathogens (e.g., *Mycobacterium tuberculosis*, *Treponema pallidum*) lack topoisomerase IV, and in the case of *M. tuberculosis,* gyrase appears to serve the decatenation function of topoisomerase IV, in addition to its own functions.[10]

Quinolones inhibit enzyme function by blocking the resealing of the DNA double-stranded break, but in addition this process stabilizes a catalytic intermediate covalent complex of enzyme and DNA that serves as a barrier to movement of the DNA replication fork[11] or transcription complexes[12] and can be converted to permanent double-stranded DNA breaks,[13] thereby functioning as topoisomerase poisons and contributing to bactericidal activity.[14] Quinolones have been shown to bind specifically to the complex of DNA gyrase and DNA rather than to DNA gyrase alone.[15,16] Single *gyrA* or *gyrB* mutants of *Escherichia coli* can produce quinolone resistance in bacteria, resistance to gyrase inhibition, and gyrase-DNA complexes with reduced quinolone binding (see "Mechanisms of Acquired Bacterial Resistance").[16] In contrast to the information for *E. coli,* which is also similar to that for other gram-negative bacteria studied, for *Staphylococcus aureus* and *Streptococcus pneumoniae* interactions of quinolones with topoisomerase IV have been shown to determine antibacterial activity by the identification of *parC* (initially named *grlA* in *S. aureus*) and *parE* (*grlB* in *S. aureus*) single mutants that have reduced quinolone activity.[17] Based on studies of mutants of this type, a general pattern has emerged. For most gram-negative bacteria, DNA gyrase is the primary quinolone target, and for many gram-positive bacteria, topoisomerase IV is the primary target, with gyrase being the secondary target. There are exceptions, however, that depend on the quinolone studied.[18,19] These patterns appear to result from the relative sensitivities of these two topoisomerases to a given quinolone, with the more sensitive of the two enzymes in a particular bacterial species defining the primary target of a particular quinolone.[20] Some quinolones under development appear to have similar potencies against both DNA gyrase and topoisomerase IV in some bacterial species.[21,22]

Quinolone inhibition of bacterial DNA replication and bacterial killing may be dissociated under some conditions, suggesting that events in addition to the initial interaction of quinolones with the topoisomerase-DNA complex may be required for cell killing.[23] In particular, inhibitors of RNA and protein synthesis reduce the bactericidal activity of some quinolones but do not affect their ability to inhibit bacterial DNA synthesis.[24] Thus inhibition of bacterial DNA synthesis per se is not sufficient to account for bacterial killing, and possibly, newly synthesized gene products may also be necessary. This effect may account for the observations that at high concentrations of quinolones, which also secondarily inhibit protein synthesis, cell killing is reduced.[5,23]

Quinolones, β-lactams, and aminoglycosides have all been shown to generate the production of hydroxyl radicals through a proposed complex series of events involving stimulation of oxidation of reduced nicotinamide adenine dinucleotide via electron transport, which generates superoxide radicals that then damage intracellular thiol-bound iron clusters, releasing ferrous iron for oxidation by the Fenton reaction. Production of hydroxyl radicals can damage cellular macromolecules and contribute to bacterial cell death, thus suggesting one component of a common pathway of bacterial lethality for different classes of bactericidal antibiotics.[25]

Eukaryotic cells also contain topoisomerases, and eukaryotic topoisomerase II, which is a homodimeric enzyme that is a member of the type IIA class of topoisomerases, such as DNA gyrase and topoisomerase IV, has a domain structure and limited primary amino-acid sequence homology similar to the bacterial enzymes.[26–28] Current antibacterial quinolones in clinical use have only minimal activity against mammalian topoisomerase II,[29] but other quinolone structures, containing a 7-hydroxyphenyl substituent or an isothiazolo ring bridging positions 2 and 3, have been shown to have substantially enhanced potency against the mammalian enzyme.[27]

MECHANISMS OF ACQUIRED BACTERIAL RESISTANCE

Bacteria acquire resistance to quinolones from spontaneously occurring mutations in chromosomal genes that either alter the target enzymes, DNA gyrase, and topoisomerase IV, or alter drug permeation across the bacterial cell membranes.[30,31] Recently, several plasmid-mediated quinolone resistance mechanisms have been identified in clinical isolates of Enterobacteriaceae. These horizontally acquired genes are generally not sufficient alone to confer clinical resistance to fluoroquinolones but enable survival under drug exposure and facilitate selection of chromosomal mutations.[32] The products of the plasmid-encoded *qnr* genes have been shown to protect DNA gyrase and topoisomerase IV from quinolone action.[33,34] A modification of a common plasmid-encoded aminoglycoside acetylating enzyme, Aac(6′)-Ib-cr, mediates quinolone resistance through acetylation of the nitrogen on the piperazinyl substituent at position 7 of ciprofloxacin and norfloxacin.[35] Genes encoding efflux pumps, such as QepA[36,37] and OqxAB,[38] that include quinolones in their substrate profiles have also been found on plasmids, albeit infrequently to date.

Resistant chromosomal mutants may be selected in the laboratory by plating bacteria on drug-containing agar. The frequency of occurrence of spontaneous mutants differs with the selecting drug concentration and the drug. For gram-negative bacteria selected with the newer fluoroquinolones, frequencies range, in general, from 10^{-6} or higher at twofold above the minimal inhibitory concentration (MIC) to undetectable ($<10^{-10}$) at 16- to 32-fold above the MIC. With a similar selection with nalidixic acid, mutants are detected more frequently when selected at a similar factor greater than the MIC because single mutations can cause a higher level of increase in resistance (>30-fold) relative to ciprofloxacin (eightfold) and other fluoroquinolones. This difference results in part because the magnitude of the increase in resistance conferred by a single-target mutation is modified by the interaction of drug with the second target enzyme. For example, for nalidixic acid, which has little activity against topoisomerase IV, a common mutation in the GyrA subunit of DNA gyrase causes a 30-fold increase in the MIC. In contrast, for ciprofloxacin, which has activity against topoisomerase IV (albeit less than its activity against gyrase), the same *gyrA* gene mutation causes only an eightfold increase in the MIC, despite

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the fact that both drugs exhibit similar loss of activity against purified DNA gyrase reconstituted with the resistant GyrA subunit.[39] Thus quinolone interaction with a second target enzyme puts a ceiling on the magnitude of the increase in resistance caused by mutation in the first enzyme target. For some quinolones that have similar potency against both target enzymes, frequencies of selection of first-step mutants may be particularly low because single-target mutations produce little or no increment in resistance.[40] Thus, for such quinolones, mutations in both targets are needed to produce substantial increments in the MIC. Serial passage of bacteria with increasing concentrations of quinolones selects mutants with high levels of resistance resulting from the additive effects of multiple mutations involving both enzyme targets.[41]

Alterations in the A subunit of DNA gyrase that cause quinolone resistance have been defined in a substantial number of clinical and laboratory isolates of *E. coli.* These alterations are clustered between amino acids 67 and 106 in the amino terminus of the A protein near the active site of the enzyme (tyrosine-122).[31] In particular, changes in serine-83 (to leucine or tryptophan) are most common and cause the largest increment in resistance, as well as reduced binding of drug to the gyrase-DNA complex in vitro. Leucine-83 causes a 128-fold increase in resistance to nalidixic acid but lesser increases in resistance to the newer fluoroquinolones (16- to 32-fold), thus likely accounting for the greater ease of selection of resistant mutants with nalidixic acid. Similar changes in the A subunit have been associated with resistance in many species of gram-negative bacteria. Single amino-acid changes in the midportion of the gyrase B protein have also been found to cause lower levels of resistance to nalidixic acid and fluoroquinolones.[31,42]

Resistance mutations in the *parC* gene of topoisomerase IV in *S. aureus* and *S. pneumoniae* have been most commonly found at position 80, in which a wild-type serine (homologous to serine-83 of DNA gyrase) is replaced by phenylalanine or tyrosine.[17,43] These mutations cause eightfold increases in resistance to several fluoroquinolones. Resistance mutations have also been found less commonly in the *parE* gene, often in positions similar to those of resistance mutations in *gyrB*.[31]

Stepwise increasing resistance occurs by sequential mutations in the *gyrA* (or *gyrB*) and *parC* (or *parE*) genes, with the first target mutation occurring in a gene for the more sensitive target enzyme. In the most highly resistant clinical strains of both gram-positive and gram-negative bacteria, one or more mutations in both *gyrA* and *parC* have been found commonly. Some species, including *M. tuberculosis, Helicobacter pylori,* and *T. pallidum,* appear to lack genes for topoisomerase IV.[31] Thus target resistance may occur more readily in the absence of a second drug target to limit the effects of resistance mutations in gyrase.

The routes of quinolone permeation across bacterial cell membranes are not fully defined, but the hydrophilic quinolones appear to diffuse across the gram-negative bacterial outer membrane through porin channels. In *E. coli* and *Pseudomonas aeruginosa,* resistance mutations in genes that affect expression of outer membrane proteins have been described.[44,45] In both cases, resistance cannot be explained by reduced diffusion alone, and reduced drug accumulation in some mutants is energy dependent, being abolished by agents that collapse the proton gradient across the membrane. In *E. coli,* resistance of multiple antibiotic resistance mutants, which exhibit reduced porin channels, is dependent on the AcrAB efflux pump, which is linked to the TolC outer membrane protein.[46,47] Overexpression of AcrAB has also been associated with quinolone resistance in clinical isolates.[48] In *P. aeruginosa,* resistance has been shown to be caused by increased expression of one of several sets of three genes that encode an efflux pump in the inner membrane, a periplasm-spanning membrane fusion protein, and a linked outer membrane protein (e.g., MexAB-OprM, composed of the MexA membrane fusion protein, MexB inner membrane efflux pump, and OprM outer membrane protein).[31,44,49] Such increased expression of one or more pump complexes is found commonly along with *gyrA* mutations in quinolone-resistant clinical isolates of *P. aeruginosa.*[50] AcrAB and MexAB are members of the resistance-nodulation-division (RND) family, which are common in gram-negative bacteria. Other RND pumps that confer quinolone resistance include MexCD-OprJ, MexEF-OprN, and MexXY-OprM (*P. aeruginosa*),[51] AcrAB homologs (*Salmonella* spp.[52] and *Enterobacter aerogenes*[53]), CmeABC (*Campylobacter jejuni*), OqxAB-TolC (*Klebsiella pneumoniae*),[54] AdeABC and AdeFGH (*Acinetobacter baumannii*), and SmeDEF (*Stenotrophomonas maltophilia*). Resistance in many mutants of this type is pleiotropic, with additional low levels of resistance to tetracycline, chloramphenicol, some β-lactams, and other antibiotics because of the broad substrate profiles of most such pumps; hence the term *multidrug resistance* is often applied to these efflux pumps.[44,55]

In gram-positive bacteria, which lack an outer membrane, overexpression of endogenous efflux pumps has also been shown to cause low-level quinolone resistance. The *S. aureus norA* gene encodes a native membrane protein that pumps hydrophilic quinolones, driven by the proton gradient across the cell membrane,[56] and overexpression of NorA, because of a mutation in the *norA* promoter region or in other regulators, causes resistance to norfloxacin, ciprofloxacin, and levofloxacin, in order of decreasing magnitude of the effect on MICs.[57] Some quinolones, such as moxifloxacin, are not affected by NorA overexpression. Other related pumps, such as NorB and NorC, can cause resistance to these quinolones as well.[58,59] In *S. pneumoniae,* PmrA, a pump with a structure similar to NorA, can also contribute to reduced quinolone susceptibility.[60] Reserpine, an inhibitor of several efflux pumps in gram-positive bacteria, improves MICs of some quinolones in clinical isolates of *S. pneumoniae* and viridans streptococci.[61] Other efflux transporters of the major facilitator superfamily, like NorA, NorB, and NorC, that can contribute to quinolone resistance in *S. aureus* include MdeA (norfloxacin, ciprofloxacin),[62] SdrM (norfloxacin),[63] QacB(III) (norfloxacin, ciprofloxacin),[64] and LmrS (gatifloxacin),[65] and in *Listeria monocytogenes* Lde.[66] Members of other pump families have also been shown to confer quinolone resistance, including MepA[67] in *S. aureus,* FepA in *L. monocytogenes,* PatAB[68] in *S. pneumoniae,* and SatAB[69] in *Streptococcus suis.* For reviews of clinically relevant chromosomally encoded multidrug resistance efflux pumps and their regulation, see the reviews by Piddock[55] and by Hooper and Jacoby.[30]

Regulation of expression of many pumps is complex, and overexpression has in many cases been shown to be due to mutations in specific regulators or networks of regulators.[30] Notably, expression can be selectively increased in certain infection environments and can contribute to fitness in those environments in the absence of antibiotics. In such cases, physiologic overexpression of drug resistance pumps in an infection environment could contribute to a reduced response to the affected antimicrobial, as well as discordance between determinations of bacterial susceptibility in vitro and responses to antimicrobials in vivo.

Plasmid-mediated quinolone resistance, long thought not to occur, was first identified and verified in multidrug-resistant, clinical isolates of *K. pneumoniae* from Alabama.[70] Used as donors, these isolates transferred plasmids by conjugation to a recipient laboratory *E. coli* with selection for resistance to β-lactams. Unexpectedly, the recipients acquired low-level resistance to quinolones as well. The plasmid-encoded gene responsible for quinolone resistance, *qnr,* was located on class I integrons flanked by other resistance genes, which can transfer multidrug resistance en bloc with the plasmid.[33] The gene *qnr* encodes a protein of the pentapeptide repeat family that is able to protect purified DNA gyrase and topoisomerase IV from quinolone action. How this protection occurs at the molecular level has not yet been defined. The plasmid-borne *qnr* genes currently comprise seven families—*qnrA, qnrB, qnrS, qnrC, qnrD, qnrE,* and *qnrVC*—and include multiple alleles.[71,72] The *qnr* genes have already been detected worldwide and are found in 1% to 7% of tested Enterobacteriaceae, predominantly in strains of *Enterobacter* spp., *K. pneumoniae,* and *E. coli.* Although resistance mediated by *qnr* genes alone is usually low level, *qnr* plasmids are usually found in strains of Enterobacteriaceae with additional chromosomal resistance mutations, and the presence of *qnr* has been shown to increase the frequency of selection of these mutations, presumably by reducing the quinolone therapeutic index.[73]

Resistance mediated by a fluoroquinolone-modifying enzyme has also been reported. A variant of the gene encoding aminoglycoside acetyltransferase Aac(6′)-Ib was able to reduce the activity of ciprofloxacin by *N*-acetylation at the amino nitrogen on its piperazinyl substituent.[35] The increase in the MIC conferred by Aac(6′)-Ib-cr was smaller than that conferred by Qnr proteins, and it was selective only for ciprofloxacin and norfloxacin, as predicted by their chemical structure. Other quinolones lacking an unsubstituted piperazinyl nitrogen were unaffected

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(see Fig. 35.1). Although the increase in the MIC of ciprofloxacin and norfloxacin was modest (threefold to fourfold), the effect on mutant prevention concentration was marked and facilitated selection of resistant clones of wild-type *E. coli* at 1.6 µg/mL, a level approximating the peak serum concentration of free ciprofloxacin during therapy.[35] The gene *aac(6′)-Ib-cr*, like the *qnr* genes, is now common worldwide and also associated with multidrug resistance.

Recently a second plasmid-encoded quinolone-modifying enzyme was reported.[74] The gene *crpP* was found on a plasmid in a clinical isolate of *P. aeruginosa* and when cloned in *E. coli* conferred a selective eightfold increase in resistance to ciprofloxacin but not other quinolones. Purified CrpP phosphorylated the carboxyl group of ciprofloxacin in an ATP-dependent fashion, and the phosphorylated ciprofloxacin was followed by subsequent degradation steps. The extent to which *crpP* is found in clinical isolates and its contribution to ciprofloxacin resistance in *P. aeruginosa* remains uncertain.

Two plasmid-mediated quinolone efflux pumps have also been found: OqxAB, which confers resistance to the antibiotic olaquindox (a quinoxaline derivative that is used in agriculture as a veterinary growth promoter) as well as an increased MIC to nalidixic acid and ciprofloxacin, and QepA, which mediates increased resistance to several antibiotics, including ciprofloxacin and erythromycin.[75,76]

ANTIMICROBIAL ACTIVITY

Current quinolones are most active against aerobic gram-negative bacilli, particularly members of the family Enterobacteriaceae and *Haemophilus* spp., and against gram-negative cocci, such as *Neisseria* spp. and *Moraxella (Branhamella) catarrhalis* (Table 35.1).[77–80] Relative to nalidixic acid, the fluoroquinolones also have additional activity against gram-negative bacilli, such as *P. aeruginosa* (see Table 35.1), and against staphylococci (Table 35.2). Ciprofloxacin remains the most potent marketed fluoroquinolone against gram-negative bacteria, and it and levofloxacin in the United States and sitafloxacin in Japan are the only available quinolones with sufficient potency for use against susceptible strains of *P. aeruginosa*. Resistance may emerge easily, however, when these quinolones are used alone for treatment of serious pseudomonal infections. For norfloxacin, ciprofloxacin, and ofloxacin, activity against streptococci and many anaerobes is limited (Table 35.3; see also Table 35.2). Agents released subsequently in the United States—levofloxacin, gatifloxacin (marketed as an ophthalmic solution), moxifloxacin, gemifloxacin, and delafloxacin—however, have greater potency against these organisms, with gemifloxacin and delafloxacin being especially potent against *S. pneumoniae* and *S. aureus,* respectively. For the fluoroquinolones that are used for treatment of infections outside the urinary tract, the MICs listed in Table 35.1 should be interpreted in relation to peak drug concentrations in serum, which range from 1.1 to 6.4 µg/mL (with usual dosing), and in relation to drug concentrations in urine that are manyfold higher for most quinolones, except those that are largely excreted by nonrenal mechanisms (see "Pharmacology"). For highly susceptible organisms, MICs may be 10- to 30-fold below achievable serum concentrations. Oral ciprofloxacin and levofloxacin are recommended for prophylaxis of anthrax, with potential similar efficacy and toxicity to doxycycline. For treatment of severe anthrax disease, parenteral fluoroquinolones are favored over doxycycline.[81] It should be noted that quinolone resistance can be selected for in *Bacillus anthracis.*[82] Thus efficacy may not be predicted in the unfortunate case of use of *B. anthracis* as an agent of bioterrorism. Among the currently available fluoroquinolones with activity against *S. aureus,* only delafloxacin exhibits a low probability for selection of resistant mutants and is thus recommended for skin and soft tissue infections.

Fluoroquinolones also have activity against mycobacteria (see Table 35.3).[77,83] Ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin are active against *M. tuberculosis, Mycobacterium fortuitum, Mycobacterium kansasii,* and some strains of *Mycobacterium chelonae* but, except for moxifloxacin, have only fair or poor activity against *Mycobacterium avium-intracellulare* complex. Ofloxacin and pefloxacin have activity against *Mycobacterium leprae* in animal models. Inclusion of fluoroquinolones added to the bactericidal activity but failed to contribute to shortening the duration of treatment for pulmonary tuberculosis,[84,85] or improve survival in tuberculous meningitis.[86,87]

Other bacteria are also inhibited by quinolones in vitro (see Table 35.1).[88] Ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin, and delafloxacin all have activity against the agents of atypical pneumonias, including *Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae,* and against genital pathogens, such as *Chlamydia trachomatis, Ureaplasma urealyticum,* and *Mycoplasma hominis. Treponema pallidum* is resistant to ofloxacin in animal models, and no other quinolone has been shown to have activity against this spirochete. Moxifloxacin, delafloxacin, and sitafloxacin among available quinolones have increased potency against anaerobes.

Activity in vitro is reduced in the presence of urine but generally not in the presence of serum. Activity is also reduced at pH values below 7 and in the presence of magnesium concentrations at 8 to 16 mM. Both of these factors often contribute to the reduced quinolone activity observed in the presence of urine. Unlike other fluoroquinolones, delafloxacin is weakly acidic, thus providing enhanced antibacterial potency and reducing the MICs of pathogens in environments with lower pH. Low pH and elevated concentrations of magnesium are associated with reduced drug accumulation in *E. coli.*[78]

Minimal bactericidal concentrations of quinolones are usually within twofold to fourfold of the MIC, and the magnitude of bacterial killing increases with further increases in drug concentration, reaching a maximum at about 30-fold above the MIC. Above this maximal killing concentration, paradoxical reductions in killing are observed and are associated with additional inhibition of protein synthesis by high concentrations of quinolones.[5,89]

The postantibiotic effect (PAE) is the period of time required for bacteria surviving a brief exposure to an antimicrobial agent to resume growth. Although PAE may be relevant in estimating the proper interval for drug dosing, its clinical importance, which may be greatest in patients with compromised host defenses, has not been proved. For quinolones, the duration of PAE has been in the range of 1 to 2 hours and tends to increase with increasing drug concentrations and length of drug exposure.

Combinations of quinolones with other antimicrobial agents have been extensively studied, and interactions with β-lactams and aminoglycosides, as measured by fractional inhibitory or bactericidal concentrations or time-kill curve studies, have generally been found to be indifferent or additive.[77] Synergistic interactions were found in a minority of strains, although for *P. aeruginosa* in some studies, synergy was seen in a substantial minority (30%–50%) of strains, including those already lacking susceptibility to one or both drugs.[90–92] Antagonistic interactions of quinolones with other antimicrobial agents have been rare. Rifampin reduced the bactericidal activity of ciprofloxacin against *S. aureus* and of moxifloxacin against *M. tuberculosis* in some studies.[93,94]

PHARMACOLOGY

Absorption

The quinolones are well absorbed from the upper gastrointestinal tract, with bioavailability exceeding 50% for all compounds and approaching 100% for several (Table 35.4).[95,96] Peak concentrations in serum are usually attained within 1 to 3 hours of administering a dose. Neither food nor achlorhydria substantially affects the extent of quinolone absorption, but food may delay the time to reach peak drug concentrations in serum.[97,98] Enteral feedings given orally, however, may reduce absorption.[99] Absorption is good when ciprofloxacin is given by nasogastric or jejunostomy tube[100] but may be decreased by concurrent enteral feedings given through these tubes.[99]

Peak fluoroquinolone concentrations in serum, after a 200-mg to 500-mg dose, range from 1.4 to 1.5 µg/mL for gemifloxacin and norfloxacin to 5.7 and 7.45 µg/mL for levofloxacin and delafloxacin, respectively (see Table 35.4). A 1-g dose of nalidixic acid produces concentrations of 20 to 50 µg/mL of serum. Drug binding to serum proteins (see Table 35.4) is generally low (30%–50%) but is higher for gemifloxacin (55%–72%) and delafloxacin (84%).

Distribution in Tissues

The volumes of distribution of quinolones are high and in most cases, with the exception of delafloxacin, exceed the volume of total body water (see Table 35.4), indicating accumulation in some tissues.

Text continued on p. 436

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TABLE 35.1 Activity of Selected Quinolones Against Selected Gram-Negative, Mycoplasmal, and Chlamydial Pathogens in vitro

	REPRESENTATIVE MIC_{90} (range) (μg/mL)[a,b]									
ORGANISM	**Nalidixic Acid**	**Norfloxacin**	**Pefloxacin**	**Ciprofloxacin**	**Ofloxacin**	**Levofloxacin**	**Gatifloxacin**	**Moxifloxacin**	**Gemifloxacin**	**Delafloxacin**
Acinetobacter spp.	(32–256)	(8–64)	(1–8)	0.25–2 (0.25–>128)	0.25–>8	0.05–32	0.03–8	>0.25–16	4–32 (0.008–32)	>4 (0.015–>4)
Aeromonas spp.	0.5	0.03	0.03	0.008–≤0.06	0.03–≤0.06	≤0.015–0.03	0.03	0.03	0.03	—
Burkholderia cepacia	16	8 (8–50)	—	(2–>256)	4–25	128 (2–256)	128 (2–256)	128 (1–256)	32 (2–64)	16 (0.25–16)
Campylobacter jejuni	8 (4–64)	(0.25–2)	0.5	0.03–64	0.25–32	0.12–32	0.25–4	0.06–0.13	—	—
Chlamydia pneumoniae	—	—	—	2	1	0.5–1	0.12	0.06–1	0.25	0.125
Chlamydia trachomatis	—	≥16	—	0.5–2	2 (0.25–4)	0.25–0.5	0.06	0.06 (0.015–0.12)	—	
Citrobacter spp.	8	0.5 (<0.25–50)	0.4–1	0.06–0.25	0.25–1	0.5 (0.12–4)	0.25–2	0.25–2	2 (0.004–16)	2 (0.008–>4)
Enterobacter aerogenes	8	0.5 (0.2–2)	0.25	0.5 (0.03–>16)	0.25 (0.1–1)	0.5 (0.06–16)	1 (1–16)	2 (0.25–>16)	0.25 (0.008–2)	0.5–2 (0.02–>16)
Enterobacter cloacae	8	0.5 (<0.25–2)	0.5	0.25 (0.025–2)	1 (0.12–1)	0.5 (0.05–2)	0.5 (0.06–1)	1 (0.06–2)	0.25–1 (0.008–16)	0.5–2 (0.02–>16)
Escherichia coli	4 (1–8)	0.12 (0.016–0.5)	0.12–0.25	0.25 (0.004–>128)	0.25 (0.032–0.25)	0.5 (0.016–32)	0.25 (0.004–8)	0.25 (0.016–32)	0.016–0.03 (0.004–32)	4 (0.004–16)
Haemophilus influenzae	0.5–4	0.06	0.06	≤0.004–0.032	0.016–0.12	0.008–0.064	0.004–0.032	0.008–0.125	≤0.004–0.032	≤0.004–0.25
Klebsiella pneumoniae	8–16	0.5 (0.2–2)	2 (0.5–2)	0.5 (0.008–>64)	2 (0.03–>64)	0.5 (0.03–>64)	1 (0.016–>64)	1 (0.03–>64)	0.25 (0.06–>32)	(0.03–>4)
Legionella spp.	1	(0.2–2)	—	0.016–0.06	0.03–0.12	0.016–0.03	0.03	0.06	0.003–0.03	0.12
Moraxella catarrhalis	2	0.4	0.25	≤0.015–0.12	0.06–0.12	≤0.03–≤0.5	≤0.03–0.05	≤0.015–0.12	≤0.004–0.015	(0.004–0.06)

Continued

TABLE 35.1 Activity of Selected Quinolones Against Selected Gram-Negative, Mycoplasmal, and Chlamydial Pathogens in vitro—cont'd

	REPRESENTATIVE MIC_{90} (range) (μg/mL)[a,b]									
ORGANISM	**Nalidixic Acid**	**Norfloxacin**	**Pefloxacin**	**Ciprofloxacin**	**Ofloxacin**	**Levofloxacin**	**Gatifloxacin**	**Moxifloxacin**	**Gemifloxacin**	**Delafloxacin**
Morganella morganii	8	0.12 (<0.06–25)	(0.25–4)	0.06 (0.015–1)	0.25 (0.12–0.25)	0.12 (0.06–1)	0.5 (0.25–2)	0.5 (0.13–4)	0.12 (0.016–8)	0.25 (0.06–0.25)
Mycoplasma hominis	>256	8–16	4	0.5–4	0.5 (0.25–4)	0.25 (0.03–2)	0.12 (0.03–0.25)	0.06 (0.03–0.25)	0.06 (0.015–0.12)	0.016 (0.008–0.016)
Mycoplasma pneumoniae	—	12	4	0.5–4	1	0.5–2.5	0.13–0.5	0.12–0.3	0.25	0.5 (0.06–0.5)
Neisseria gonorrhoeae	1	0.06	0.06	0.001–2	0.03–2	≤0.008–2	0.004–0.025	0.015–1	—	0.125 (0.001–0.25)
Neisseria meningitidis	0.5	0.03	0.03	0.004–0.008	0.03	≤0.008–0.016	≤0.008	≤0.008–0.016	0.002	0.001
Proteus mirabilis	8	0.1 (0.064–0.5)	0.25	0.12 (0.008–>4)	0.25 (0.064–0.5)	0.12 (0.032–>4)	0.25 (0.032–>4)	0.5 (0.064–16)	0.12–0.5 (0.032–8)	(0.064–2)
Proteus vulgaris	8	0.1 (0.12–0.5)	0.25	0.06 (0.008–0.12)	0.5 (0.032–0.5)	0.12 (0.016–0.25)	0.39 (0.032–0.5)	1 (0.032–1)	0.12 (0.032–0.5)	—
Providencia rettgeri	16	2 (0.25–3.1)	0.5	0.5 (0.025–4)	2–4	1 (0.1–4)	0.5	1 (0.5–2)	—	>1–4
Providencia stuartii	32	2 (<0.25–2)	4	4–8 (0.12–>16)	>8 (1–>16)	4 (0.25–>16)	0.5	1 (0.5–2)	0.25–16 (0.015–1)	>1–4
Pseudomonas aeruginosa	16	2 (2–16)	2	0.032–128	0.125–>128	0.125–128	>4–32	0.125–>128	4–8 (0.032–256)	0.25–>4
Salmonella spp.	2–4	≤0.06 (≤0.06–0.25)	0.12	0.01–0.25	0.12–0.5	0.03–0.25	0.06–0.25	0.12–0.25	0.015–0.12	(0.004–8)
Serratia marcescens	≥100	1 (0.025–50)	1 (1–8)	2 (0.5–12.5)	4 (1–25)	2 (0.25–8)	4 (2–12.5)	4 (0.5–8)	1–2 (0.008–4)	—
Shigella spp.	8	≤0.06–0.12	0.25	0.008–≤0.06	0.06–0.12	0.016–0.03	0.016–0.03	0.03–0.06	≤0.015–0.25	
Stenotrophomonas maltophilia	16	2 (2–25)	4	>2–32	8–64	2–32	2–32	1–128	4 (0.016–16)	(0.12–16)
Yersinia enterocolitica	2	≤0.12	0.25	0.016–0.06	0.12–0.25	0.03–0.06	0.06	0.06–0.12	0.015–0.03	

[a] MIC_{90}, Minimal inhibitory concentration for 90% of strains.
[b] Resistance has been increasing in many hospital pathogens over time. Therefore it is important to consult individual antibiograms, because resistance can vary among institutions.
Data from references 77, 78, 80, 88, and 546–552.

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TABLE 35.2 Activity of Selected Quinolones Against Selected Gram-Positive Bacteria in vitro

ORGANISM	REPRESENTATIVE MIC_{90} (range) (μg/mL)[a]									
	Nalidixic Acid	Norfloxacin	Pefloxacin	Ciprofloxacin	Ofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin	Gemifloxacin	Delafloxacin
Staphylococcus aureus—methicillin susceptible	100	2 (1–4)	0.5 (0.1–2)	0.5 (0.03–2)	0.5 (0.25–1)	0.25 (0.25–0.5)	0.12 (0.10–0.25)	0.12 (0.06–0.25)	0.06 (0.03–0.06)	0.008 (0.002–4)
Staphylococcus aureus—methicillin resistant	—	—	—	≥32 (25–128)	32 (62.5–50)	16 (8–>32)	16 (4–>32)	4 (2–16)	8 (1–8)	0.5 (0.004–4)
Coagulase-negative staphylococci—methicillin susceptible	100	2 (0.4–>4)	1 (0.5–4)	2 (0.25–16)	0.5	1 (0.25–2)	(0.25–4)	0.13 (0.12–1)	0.3 (0.015–0.03)	0.5 (0.002–1)
Coagulase-negative staphylococci—methicillin resistant	—	—	—	>16 (0.39–64)	32 (>8–32)	(0.39–16)	(0.25–8)	4 (0.13–8)	2 (0.25–2)	(0.12–2)
Streptococcus pneumoniae	>128	16 (4–16)	12 (8–16)	2 (1–8)	2 (1–8)	1 (1–2)	0.5 (0.25–1)	0.25 (0.06–0.5)	0.06 (0.03–0.06)	0.015 (0.004–0.12)
Streptococcus pyogenes	>100	4 (2–16)	8 (8–16)	2 (0.5–3.1)	2 (1–4)	1 (0.5–2)	0.5 (0.39–0.5)	0.25 (0.12–0.25)	0.06 (0.015–0.06)	0.015 (0.001–0.03)
Streptococcus agalactiae	>128	16 (4–16)	32	2 (0.5–2)	4 (1–4)	1	0.5	0.5 (0.12–0.5)	0.12 (0.03–0.25)	0.015 (0.001–0.5)
Streptococcus spp.	>64	16 (4–32)	>12.5	4 (1–8)	4 (2–8)	2 (1–2)	0.5 (0.5–1)	0.25 (0.25–2)	0.12	0.03 (0.004–2)
Enterococcus faecalis	>64	8 (4–32)	4–8	(1–128)	(2–32)	(2–50)	(1–>4)	(0.5–16)	2 (2–4)	1 (0.004–2)
Enterococcus faecium	>64	≥12.5	—	(2–>128)	(4–100)	(2–64)	(3–>32)	(4–≥32)	8	(0.008–>4)
Listeria monocytogenes	>64	8 (4–16)	6–8	1 (0.5–4)	4 (2–4)	1 (1–2)	0.5	0.5	0.25 (0.12–0.25)	0.12 (0.06–0.12)
Corynebacterium spp.	—	4 (4–>128)	8 (8–>128)	1 (0.05–128)	1 (0.5–64)	(2–>16)	>4	2	(0.5–16)	—
Bacillus spp.	—	1	—	0.25 (0.06–1)	0.5	0.25 (0.06–2)	0.25	—	—	—
Nocardia spp.	>128	64	64	(1.4–>25)	(2.6–>25)	(0.12–>32)	—	(0.03–32)	(0.03–32)	—

[a]MIC_{90}, Minimal inhibitory concentration for 90% of strains.
Data from references 77, 78, 547, 548, and 552–555.

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TABLE 35.3 Activity of Selected Quinolones Against Selected Anaerobic Bacteria and Mycobacteria in vitro

	REPRESENTATIVE MIC_{90} (μg/mL)[a]									
ORGANISM	**Nalidixic Acid**	**Norfloxacin**	**Pefloxacin**	**Ciprofloxacin**	**Ofloxacin**	**Levofloxacin**	**Gatifloxacin**	**Moxifloxacin**	**Gemifloxacin**	**Delafloxacin**
Bacteroides fragilis	512	>128	16	4–64	2–12.5	2–>16	0.25–8	0.5–8	0.5–4	0.12
Bacteroides spp.	512	128	—	16–>64	2–32	4–16	2–8	8	—	
Fusobacterium spp.	256	16	32	2–4	2–16	0.39	—	2	0.5	0.015
Clostridium spp.	256	2	1	1–16	1–8	0.12–4	—	—	—	
Clostridium perfringens	64	8	8	0.5–1.56	0.5–8	0.39	0.39–1	1	0.12	0.008
Clostridioides difficile (formerly *Clostridium difficile*)	>128	128	64	6.25–12.5	12.5–16	6.25–128	1.56–2	2–16	2	(0.015–2)
Anaerobic gram-positive cocci	256–512	16–64	16	2–6.25	2–8	0.32–4	2	0.5–2	0.125–0.5	0.03
Mycobacterium tuberculosis	—	8	8	1	0.8–1.3	0.25–1 (<0.032–16)	0.12–0.5	0.125–0.5 (<0.032–4)	8	0.78–6.25
Mycobacterium avium complex	—	≥16	>64	16	10–100	0.5–64	0.5–32	0.5–16	—	25
Mycobacterium chelonae	—	>16	>64	8	>20	4–128	4–64	8–64	—	
Mycobacterium fortuitum	—	2	2	0.3	1–3.2	0.06–2	0.03–0.25	0.06–0.5	—	
Mycobacterium kansasii	—	8	4	8	1–3.2	0.25	—	—	—	

[a] MIC_{90}, Minimal inhibitory concentration for 90% of strains.
Data from references 77, 78, and 556–559.

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TABLE 35.4 Pharmacokinetics of Selected Quinolones

PHARMACOKINETIC PARAMETER	NORFLOXACIN	PEFLOXACIN	CIPROFLOXACIN	OFLOXACIN	LEVOFLOXACIN	MOXIFLOXACIN	GEMIFLOXACIN	DELAFLOXACIN
Dose (mg) PO	400	400	500	400	500	400	320	450
C_{max} (μg/mL) PO	1.5	3.2	2.4	4.6	5.7	4.3	1.4	7.45
Dose (mg) IV	—	400	400	400	500	400	—	300
C_{max} (μg/mL) IV	—	5.8	3.4–6.7	5.5	5.7	4.5	—	9.29
Serum protein binding (%)			30	30	24–52	39–52	55–73	84
Half-life (h)	3.3	11	4	4–5	6–8	9.5	7	4–8.5
Bioavailability (%)	(50)	>95	70	>95	99	86–100	71	59
V_D (L)	—	112	231	102	102	122	280	30–48
Cl_r (mL/min)	234	20	358	195	116	30	193	109
Renal excretion (%)	27	—	40	73	77	20	36	35–45

C_{max}, Peak serum concentration; *Cl_r*, renal clearance; *IV*, intravenous; *PO*, oral; *V_D*, volume of distribution.

Concentrations in prostate tissue, stool, bile, lung, and neutrophils and macrophages usually exceed serum concentrations (Table 35.5). Concentrations in urine and kidney tissue are high for quinolones with a major renal route of elimination, particularly so for levofloxacin and substantially less for moxifloxacin, which has a major route of nonrenal elimination. Concentrations of quinolones in saliva, prostatic fluid, bone, and cerebrospinal fluid (CSF) are usually lower than drug concentrations in serum. Active transport systems appear to be involved in reducing concentrations of levofloxacin in CSF.[101] Fluoroquinolones vary in terms of penetration into the CSF. Their penetration into the CSF in the absence of meningeal inflammation is, however, much higher than that of β-lactam antibiotics.[102] In patients with tuberculous meningitis, CSF penetration (AUC_{CSF}/AUC_{plasma} ratio) of levofloxacin was similar to that of moxifloxacin and greater than that of ciprofloxacin.[103,104] Penetration into ascitic fluid in patients with liver failure has been found for ofloxacin (120%).[105] Penetration into human breast milk has also been documented for ciprofloxacin and ofloxacin.[106]

Elimination

The terminal half-lives of elimination from serum range from 3 hours for norfloxacin and ciprofloxacin to 12 hours for moxifloxacin, allowing twice- or once-daily dosing (Table 35.6; see also Table 35.4). The principal routes of elimination differ among quinolones. Ofloxacin, levofloxacin, and sitafloxacin are eliminated predominantly by the kidneys, and nalidixic acid and moxifloxacin are eliminated predominantly by nonrenal pathways. Most other quinolones have mixed excretion by both renal and nonrenal routes.

Renal clearances of norfloxacin, ciprofloxacin, ofloxacin, sitafloxacin, and levofloxacin exceed glomerular filtration rates, indicating net tubular secretion. In support of tubular secretion, renal clearances of norfloxacin and ciprofloxacin are reduced by probenecid, but drug accumulation does not occur. In contrast, the renal clearance of pefloxacin is below or equal to the glomerular filtration rate, suggesting net tubular reabsorption.[107]

TABLE 35.5 Body Tissues, Fluids, and Cells in Which Quinolone Concentrations Exceed Quinolone Concentrations in Serum

SITE	FOLD INCREMENT
Prostate tissue	0.9–2.3
Feces	100–1000
Bile	2–20
Lung tissue	1.6–6
Macrophages and neutrophils	2–>100

Hepatic metabolism accounts for the majority of the elimination of moxifloxacin and nalidixic acid. In the latter case, however, active metabolites contribute to antibacterial effects. The hydroxynalidixic derivative of nalidixic acid is more active than its parent compound. The metabolites and inactive glucuronide conjugate to the 3-carboxyl group are excreted in the urine. Conversion of norfloxacin, ciprofloxacin, and delafloxacin to less active metabolites accounts for 10% to 20% of elimination. There is minimal hepatic biotransformation (<10%) of ofloxacin and levofloxacin. Hepatic metabolism and biliary excretion are the principal routes of elimination of moxifloxacin (>60% of dose; 38% sulfoconjugation, 14% glucuronide conjugation). In addition to glucuronide conjugates and desmethylpiperazinyl derivatives, other metabolites of quinolones that have been identified have had predominantly alterations of the piperazine ring, including *N*-oxide, *N*-sulfo, *N*-formyl, and desethylene derivatives.[95,107]

Transintestinal secretion has been identified after intravenous (IV) administration of ciprofloxacin and accounts for about 10% to 15% of drug excretion,[107] and this effect may be mediated by P-glycoprotein and other intestinal transporters.[95]

Dosage Adjustments in Renal and Hepatic Insufficiency

As expected from differences in the routes of excretion, increases in drug half-life in the presence of severe renal insufficiency are greatest for ofloxacin and levofloxacin (fourfold to fivefold) and least for moxifloxacin (no change), with other quinolones exhibiting intermediate effects (about twofold). To prevent excessive drug accumulation, dosage reduction (increase in the dose interval from 12 to 24 hours or halving the daily dose for those quinolones normally given once daily; see Table 35.6) is indicated at creatinine clearances below 50 mL/min for ofloxacin and levofloxacin, below 40 mL/min for gemifloxacin, and below 30 mL/min for norfloxacin, ciprofloxacin, and delafloxacin. For delafloxacin, dose reduction is advised for the intravenous formulation because of concern over potential toxicities associated with accumulation of the intravenous vehicle, sulfobutylether-β-cyclodextrin. No dosage reduction is indicated for nalidixic acid and moxifloxacin. Clearance by hemodialysis is low (<14% of plasma clearance) for norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin.[108] Similarly, peritoneal dialysis contributes little to the clearance of ciprofloxacin and ofloxacin.[109] Continuous venovenous hemofiltration in patients with severe renal failure constitutes 16% to 70% clearance of levofloxacin, 6% to 37% clearance of ciprofloxacin,[110,111] and about 9% clearance of moxifloxacin.[112] In patients on continuous venovenous hemofiltration, levofloxacin is dosed at 250 mg/day and ciprofloxacin at 400 mg/day. No dose adjustment is needed for moxifloxacin.

Fewer data are available on the effects of hepatic insufficiency on quinolone half-lives, but there is no need for dosage adjustments of norfloxacin, ciprofloxacin, ofloxacin, moxifloxacin, and delafloxacin.[113]

TABLE 35.6 Dosing of Quinolones in Patients With Normal and Reduced Renal Function

	NORMAL RENAL FUNCTION		RENAL FAILURE WITH GFR (mL/min)		
QUINOLONE	Oral	Intravenous	10–50	<10	REMOVAL BY DIALYSIS
Norfloxacin	400 mg q12h	—	1×dose q24h	1×dose q24h	No (H, P)
Pefloxacin	400 mg q12h	400 mg q12h	No change	No change	No (H)
Ciprofloxacin	250–750 mg q12h	200–400 mg q12h	1×dose q18h	1×dose q24h	No (H, P)
Ofloxacin	200–400 mg q12h	200–400 mg q12h	1×dose q24h	½ dose q24h	No (H, P)
Levofloxacin	250–750 mg q24h	250–750 mg q24h	½ dose q24h	½ dose q48h	No (H, P)
Moxifloxacin	400 mg q24h	400 mg q24h	No change	No change	No (H, P)
Gemifloxacin	320 mg q24h	—	½ dose q24h	½ dose q24h	20%–30% (H)
Delafloxacin	450 mg q12h	300 mg q12h	Below 30 mL/min switch to oral therapy	Not recommended	19% (H)[a]

[a]Intravenous vehicle (sulfobutylether-β-cyclodextrin) is also removed by hemodialysis.
GFR, Glomerular filtration rate; *H,* hemodialysis; *P,* peritoneal dialysis.

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Changes in renal function that accompany severe liver disease may, however, affect ciprofloxacin and ofloxacin elimination to a lesser extent.

Interactions With Other Drugs

When coadministered by mouth with aluminum-, magnesium-, or, to a lesser extent, calcium-containing antacids, quinolones have markedly reduced oral bioavailability, presumably because of the formation of cation-quinolone complexes that are poorly absorbed.[114,115] Sucralfate, which contains large amounts of aluminum ions, also reduces absorption of quinolones. Tablets should be taken at least 2 hours before or 2 to 6 hours after these drugs. In general, histamine type 2 receptor antagonists and proton pump inhibitors do not have important effects on absorption of quinolones. Concurrent administration of quinolones with iron sulfate, multivitamin-mineral regimens containing zinc, and the buffered formulation of dideoxyinosine has also been reported to reduce quinolone absorption.[116] Nutritional supplements given by nasogastric tube may reduce the absorption of quinolones given concurrently by the same route, probably because these supplements also contain multivalent cations such as iron and zinc. Concomitant administration of morphine decreases maximal serum concentrations of oral ciprofloxacin by 35% to 50%.

For intravenous formulations of ciprofloxacin, precipitates have been reported when these quinolones were infused through the same intravenous tubing with aminophylline, amoxicillin with and without clavulanate, or flucloxacillin. Separate infusions are indicated.

Quinolones vary in the extent to which they impair the elimination of the methylxanthines theophylline and caffeine. The effects appear to result from inhibition by some quinolones of hepatic cytochrome P-450 isozyme 1A2 (CYP1A2),[117] which is involved in theophylline and caffeine metabolism. With ciprofloxacin, a 30% reduction in clearance and 20% to 90% increases in serum concentrations of theophylline are observed, but norfloxacin, ofloxacin, levofloxacin, moxifloxacin, and gemifloxacin had little or no effect (2%–11% increases in serum concentrations of theophylline).[115,118,119] In patients receiving ciprofloxacin in combination with theophylline, serum levels of theophylline should be monitored and reductions in the dose of theophylline considered. No such adjustments should be needed in patients receiving theophylline concurrently with other fluoroquinolones. Concurrent administration of ciprofloxacin at the usual daily dose (500 mg twice daily) with caffeine resulted in a higher peak serum concentration (C_{max}) and cumulative 24-hour serum concentration of ciprofloxacin in females relative to males. This effect, however, disappeared when parameters were corrected for body weight.[120]

Tizanidine, clozapine, and methadone are also metabolized by CYP1A2. Concomitant administration of ciprofloxacin and tizanidine may increase the central nervous system and systemic hypotensive effects of the latter.[121] Low doses of ciprofloxacin have increased serum levels of clozapine, and one patient was reported to have developed symptoms of methadone overdose while taking ciprofloxacin.[122] Thus the effects of ciprofloxacin on tizanidine, clozapine, and methadone (and possibly other drugs affected by CYP1A2, such as haloperidol, mexiletine, cimetidine, and paroxetine) should be monitored similar to those with methylxanthines.

Another hepatic P-450 isozyme, CYP3A4, is affected by many classes of antimicrobials, which can be inhibitors, inducers, or substrates of this metabolism enzyme. Such antimicrobials include macrolides, streptogramins, rifampin, azoles, and a variety of antiretroviral agents but not quinolones. Thus the occasional case reports of apparent interactions of quinolones with other drugs interacting with CYP3A4 are difficult to assess for their importance or predictive value. Such case reports include those associating ciprofloxacin with increased cyclosporine levels and nephrotoxicity or increased levels of diazepam.[115]

Moxifloxacin is coadministered with rifampicin in the treatment of mycobacterial and other bacterial infections. Increased activity of the sulfate conjugation pathway of moxifloxacin metabolism by rifampicin has been shown to reduce moxifloxacin levels, potentially associated with reduced efficacy, and may warrant an increase of moxifloxacin dosage.[123,124] In direct studies of interactions of warfarin with quinolones, no effects on coagulation tests were seen generally, and in those cases in which a drug interaction was seen (ciprofloxacin), there was an increase in the relatively inactive *R*-enantiomer of warfarin, which is metabolized by the P-450 isozyme CYP2C9, and there was no effect on the active *S*-enantiomer or prothrombin times.[125] Case reports of patients who developed bleeding while on warfarin and ciprofloxacin have appeared, however, suggesting that in uncommon special settings, quinolone promotion of an anticoagulant effect of warfarin may occur, possibly caused by other concomitant therapies, by effects on microbial flora that synthesize vitamin K in the intestine, or by changes in patients' food intake, or promoted by the underlying disease conditions or genetic predispositions, which would not be reflected in data collected in controlled clinical studies. Limited case series suggest that treatment with moxifloxacin, which has enhanced activity against anaerobic bacteria compared with either ciprofloxacin or levofloxacin, may prolong the prothrombin time earlier than the other quinolones.[126] A case-control study of continuous warfarin users older than 65 years identified an association between exposure to quinolones and an increased risk of bleeding, albeit lower than that with other antibiotics.[127] As a precaution, prothrombin times should be rechecked in patients on warfarin after initiation of quinolones or other antimicrobial agents. When mixed with heparin as a lock solution used for the treatment of catheter-related bloodstream infection, the maximum concentration of ciprofloxacin is limited because of precipitation at higher concentrations.[128]

Disturbances of glucose metabolism have been rarely reported with quinolones, but there have been case reports of elevated glyburide levels and hypoglycemia in a diabetic patient given ciprofloxacin and in several patients receiving gatifloxacin and hypoglycemic agents.[110] These effects were unexpected and not fully explained. Glyburide may be metabolized by CYP2C9, which is not known to be affected by quinolones, and when directly studied, there was no detectable effect of gatifloxacin on glyburide metabolism or glucose tolerance in diabetic volunteers. Furthermore, hypoglycemia has been reported in patients receiving gatifloxacin and clinafloxacin without concomitant hypoglycemic agents, and hyperglycemia has also been reported in patients receiving gatifloxacin. Thus effects in addition to potential drug interactions likely contribute to the occurrences (see "Adverse Events").

Nonsteroidal antiinflammatory drugs (NSAIDs) may affect the central nervous system stimulant effects of some quinolones. Seizures were reported in a group of Japanese patients receiving enoxacin and the NSAID fenbufen. Potentiation of seizures by combinations of quinolones and NSAIDs has also been reported in animals. Assays of the displacement of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) or a related molecule from GABA receptors in rat brain tissue have demonstrated displacement of GABA by quinolones and enhancement of this displacement by fenbufen and by theophylline.[127,129] Clinical experience does not suggest, however, that concurrent use of quinolones other than enoxacin with other NSAIDs will result in central nervous system toxicities, but patients receiving both classes of drugs should be cautioned about and monitored for these potential adverse effects.

Although probenecid reduces the renal clearance of norfloxacin and fleroxacin, no quinolone accumulation occurred. The effect of probenecid might be predicted to be greater with quinolones such as ofloxacin and lomefloxacin, for which renal clearance includes tubular secretion and is the predominant mode of clearance, but data are lacking.

CLINICAL USES

Earlier quinolones such as nalidixic acid, oxolinic acid, and cinoxacin were used almost exclusively for treatment of urinary tract infections, although nalidixic acid was also used for treatment of shigellosis. With the development of the more potent fluoroquinolones, an increasingly broad array of infections is treated with members of the fluoroquinolone class.

Urinary Tract Infections

Although the low pH and magnesium concentrations present in urine may reduce quinolone activity, the concentrations of many quinolones in urine are usually sufficient to provide substantial therapeutic ratios of urinary drug concentration to the MIC of most urinary pathogens.

For uncomplicated urinary tract infections, usually in symptomatic young women with cystitis caused by highly susceptible organisms such as *E. coli,* most quinolones are likely to be highly effective when given for brief courses of 3 to 10 days,[129a–129c] and norfloxacin, ciprofloxacin, and ofloxacin

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have been found to be comparable to trimethoprim-sulfamethoxazole (TMP-SMX)[129d] and nitrofurantoin[129b,129e,129f] and better than amoxicillin-clavulanate.[129g] Usually, the lowest dose in the dosage range (see Table 35.6) is sufficient for treatment of these infections. Three-day regimens of norfloxacin, ciprofloxacin, and ofloxacin result in cure rates of 81% to 96%.[129b] An extended-release formulation of ciprofloxacin (500 mg oral [PO] once daily) was comparable to conventional ciprofloxacin (250 mg PO twice daily) when both were given for 3 days.[129h,129i] Limited data on single-dose therapies with ciprofloxacin, ofloxacin, and norfloxacin indicate eradication in 75% to 96% of patients.[129j,129k] Single-dose norfloxacin (800 mg) was equivalent to a 3-day regimen for *E. coli* infections,[129l] but for *Staphylococcus saprophyticus* infections, a 7-day regimen is preferred because of failures with shorter courses.[129m,129n] Women with uncomplicated acute pyelonephritis given norfloxacin, ciprofloxacin (either orally or intravenously),[129o] or ofloxacin for 7 to 10 days have bacteriologic cure rates comparable to or better than those with TMP-SMX, and levofloxacin and ciprofloxacin were comparable to each other with 95% eradication rates.[129p,129q,130]

Increased fluoroquinolone resistance among community uropathogens and associated microbiologic and clinical failure, similar to that observed with TMP-SMX, is a major consideration when deciding to use fluoroquinolone for urinary tract infections.[131,132] A disturbing finding has been the widespread distribution of urinary tract infections caused by multidrug-resistant *E. coli* clonal groups in the United States and worldwide.[133,134] Of interest, strains belonging to this clone were found to harbor the gene *aac(6′)-Ib-cr*.[135] In addition, the potential for collateral damage (i.e., the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms) complicates the use of this antimicrobial class. The Infectious Diseases Society of America (IDSA) incorporated these considerations into their guidelines.[130] The recommended antibiotics for acute uncomplicated cystitis are nitrofurantoin, TMP-SMX, fosfomycin, or pivmecillinam, whereas a 3-day fluoroquinolone is a second-line treatment option. For acute pyelonephritis, fluoroquinolones (5–7 days) are an appropriate choice for therapy in settings where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10%.[130,136–138] Rates of resistance, however, have been higher (approaching 30%) in recently reported surveys of extraintestinal *E. coli* isolates in the United States, due in part to the emergence of the *H*30 subclone of sequence type ST131.[139] For prophylaxis of recurrent infections in women, norfloxacin (200 mg at bedtime) was highly effective and superior to nitrofurantoin,[140] and low doses of ofloxacin (100 mg), norfloxacin (200 mg), and ciprofloxacin (125 mg) given after coitus have also been effective as prophylaxis.[141] Other agents, such as nitrofurantoin or TMP-SMX, are preferred for this indication, however, because of expense, collateral damage, and the risks of potential pregnancy.

Cystitis occurring in elderly women is more often complicated by comorbid conditions and is more likely to be caused by pathogens, in addition to *E. coli,* that are less susceptible to antimicrobial agents. For such infections, ofloxacin and ciprofloxacin given for 7 days have high eradication rates but have no clear advantage over a short course.[142]

Complicated urinary tract infections occurring in men and in patients with catheters or structural or functional abnormalities of the urinary tract are often caused by more resistant pathogens and have a higher frequency of relapse and reinfection. Bacteriologic cure rates for ciprofloxacin were superior to those for TMP-SMX and aminoglycosides shortly after completion of a 7- to 10-day course, but the low fractions of patients who continued to have sterile urine were similar by 4 to 6 weeks after therapy.[138,143–145] In patients with spinal cord injury, treatment with ciprofloxacin (250 mg twice daily) for 3 and 14 days had similar clinical cure. The percentage of patients with microbiologic cure was, however, significantly higher for the 14-day treatment arm at long-term follow-up and was attributable to the significantly lower rates of both clinical and microbiologic relapse.[146] High cure rates were seen with both ofloxacin and levofloxacin.[147,148] In collected noncomparative trials, infections caused by *P. aeruginosa* were eradicated in 70% of patients given ciprofloxacin and 83% of those given norfloxacin. Development of bacterial resistance has been associated with therapeutic failure in about 2% of patients overall, but resistance rates (10%–20%) are often higher for *P. aeruginosa* infections, and resistance can be selected with fluoroquinolone therapy.[149] Ciprofloxacin is the preferred fluoroquinolone for treatment of *P. aeruginosa* infections, and when chosen, doses of at least 500 mg orally twice daily should be used. In patients with bladder dysfunction resulting from spinal cord injury who used intermittent suprapubic taps or self-catheterization for bladder emptying, ciprofloxacin (100 mg at bedtime) reduced episodes of infection about 10-fold relative to placebo.[150] Whereas infections in the placebo group represented a mixture of enteric and nonenteric bacteria and enterococci, breakthrough infections in the ciprofloxacin group were largely nonenteric bacteria, particularly *P. aeruginosa,* which were often resistant.

Fluoroquinolones are now commonly used in prophylaxis in urologic surgery. When postoperative bacteriuria, but not other secondary outcomes, was the parameter to define efficacy of antimicrobial prophylaxis, single-dose ciprofloxacin (500 mg) or levofloxacin (500 mg) has been shown to be effective after transurethral prostate resection and transrectal prostate biopsies,[151–157] but infections with quinolone-resistant *E. coli* have been seen increasingly with this use (see "Prostatitis"). There is no evidence that prophylaxis should extend beyond 24 hours after a procedure.[158,159] Prophylaxis of urinary tract infection in renal transplant recipients is routinely done because of high risk from infection. Although ciprofloxacin is effective,[160] TMP-SMX is often used because it may be additionally useful as prophylaxis against other opportunistic pathogens in this patient group.

Prostatitis

Fluoroquinolones concentrate in prostatic tissue, with lower levels in prostatic fluid. In one small comparative study of men with predominantly *E. coli* infections, norfloxacin given for 4 to 6 weeks was superior (92% eradication) to TMP-SMX (67% eradication) at 1-month follow-up.[161] In open studies, similar courses of norfloxacin, ciprofloxacin, ofloxacin, and levofloxacin have produced eradication rates of 60% to 86% at follow-up, ranging from 1 to 13 months.[162,163] Similar results were obtained with levofloxacin and prulifloxacin (a fluoroquinolone marketed outside the United States).[164] With 2-week courses of therapy and infections caused by less susceptible organisms, such as *P. aeruginosa* and enterococci, failures appear to be more frequent.[113,165] Recent studies indicate that approximately 11% to 22% of men undergoing transrectal prostate biopsy harbor fluoroquinolone-resistant organisms within the rectum before the administration of antimicrobials, and that fecal carriage of fluoroquinolone-resistant *E. coli* strains was a risk factor for infectious complications after prostate biopsy.[166,167] Fluoroquinolone-resistant *E. coli* sequence type 131 has been the predominant clone causing bloodstream infection after transrectal prostate biopsy.[166] Two strategies for the prevention of infection have recently emerged: "augmented" standard fluoroquinolone or aminoglycoside prophylaxis with a second agent, and targeted prophylaxis guided by prebiopsy screening for rectal colonization with ciprofloxacin-resistant organisms.[168–170] Although prebiopsy rectal screening is favored with respect to antibiotic stewardship goals, its implementation is more difficult to achieve.

Sexually Transmitted Diseases

Neisseria gonorrhoeae is an important pathogen in urogenital diseases, anogenital diseases, and pelvic inflammatory disease (PID). Because patients are managed on the basis of presenting symptoms and signs and associated risk factors (i.e., syndromic approach), stringent clinical efficacy criteria are used to ensure that therapy is effective against this pathogen.[171,172] After the emergence of quinolone resistance among *N. gonorrhoeae* strains, the Centers for Disease Control and Prevention (CDC), in April 2007, ceased recommending fluoroquinolones in its treatment guidelines.[173] Earlier data indicate, however, that susceptible strains can be treated with quinolones. Quinolones have retained activity in vitro against the sexually transmitted pathogens *C. trachomatis* and *Haemophilus ducreyi,* but they appear to lack activity against *T. pallidum*.[174]

Uncomplicated quinolone-susceptible gonococcal urethritis and cervicitis are effectively eradicated by single doses of quinolones (norfloxacin, 800 mg; ciprofloxacin, 250 mg; ofloxacin, 400 mg).[175,176] Rectal infections appear to have virtually complete cure rates with all of these quinolones, and pharyngeal infections are similarly highly cured by ciprofloxacin and ofloxacin.[176,177]

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Single doses of quinolones are ineffective for genital chlamydial infections.[143] Seven-day courses of therapy with norfloxacin and ciprofloxacin have failed, but 7-day courses of ofloxacin and levofloxacin were comparable to a similar course of doxycycline for treatment of chlamydial infections.[178–181] In a more recent study, sitafloxacin (which is not currently available in the United States) 100 mg twice daily for 7 days was effective against symptomatic nongonococcal urethritis in heterosexual men.[182]

Small numbers of patients with gonococcal and nongonococcal PID have been cured with 10- to 14-day courses of sequential intravenous and oral ciprofloxacin or oral ofloxacin.[183,184] Results from three more recent randomized clinical trials of treatment for PID, a syndrome with mixed microbiology, including gonococci, chlamydiae, enteric bacteria, and anaerobes, have been published. Ofloxacin (400 mg twice daily for 10 days) and cefoxitin (2 g intramuscularly [IM] once) plus doxycycline (100 mg twice daily for 10 days) were similar, and ofloxacin was highly effective in eradicating gonococci and chlamydiae.[185] Ciprofloxacin (250 mg twice daily) plus clindamycin (300 mg three times daily) given for 14 days was also comparable to ceftriaxone plus doxycycline, with high clinical cure rates, and was effective for *C. trachomatis* eradication (100% in both groups).[186] In randomized trials, moxifloxacin (400 mg once daily) monotherapy was clinically and bacteriologically as efficacious as metronidazole (500 mg twice daily) plus either ofloxacin (400 mg twice daily) or levofloxacin, with all drugs administered for 14 days.[187] In the latter trial, a single intramuscular dose of ceftriaxone was also given if *N. gonorrhoeae* was detected.

In patients with chancroid, *H. ducreyi* was eradicated from genital ulcers by ciprofloxacin (500 mg twice daily for 3 days) in all patients, a result comparable to that with TMP-SMX.[188] A once-daily dose of 500 mg or 250 mg for 5 days was effective in 88% of patients.[188] In another randomized, double-blind, placebo-controlled clinical trial, single-dose ciprofloxacin (500 mg) was comparable to a 7-day course of erythromycin (500 mg three times daily), with an overall cure rate of 92%.[189] The 3-day ciprofloxacin regimen is an option for treatment of chancroid in the CDC guidelines.[190]

Two cases of septic arthritis with susceptible gonococci have responded to ciprofloxacin. For bacterial vaginosis, ofloxacin was less effective than metronidazole.[191] There are no data on treatment of syphilis with quinolones in humans, but in experimentally infected rabbits, ofloxacin lacked efficacy.

Gastrointestinal and Abdominal Infections

Quinolones were active against all bacterial pathogens known to cause gastroenteritis, but resistance has emerged in some settings. Although fecal material may decrease the activity of quinolones, drug concentrations in feces are exceedingly high. The penetration of quinolones into macrophages (see Table 35.5) may also be important for their effectiveness in systemic *Salmonella* infections.

Bacterial gastroenteritis is often a self-limited disease, but in a number of circumstances quinolones have been shown to shorten the duration of diarrhea and to eradicate pathogens from stools.[192] In traveler's diarrhea, which is often caused by enterotoxigenic *E. coli* and *Shigella* spp., norfloxacin (400 mg twice daily for 3 days) and ciprofloxacin (500 mg twice daily for 5 days), begun shortly after the onset of diarrhea, have shortened the duration of loose stools by 1 to 3 days relative to placebo and have been comparable to TMP-SMX.[193,194] Because of resistance to TMP-SMX among *E. coli* in many parts of the developing world, quinolones are often the preferred therapeutic agents in travelers.[195] Single-dose therapies, including ciprofloxacin (500 mg or 1 g)[196,197] and ofloxacin (400 mg),[198] are also effective with or without loperamide for this indication. After the emergence of quinolone resistance, the combination of levofloxacin and loperamide was evaluated in adult US military personnel or their families located in Turkey and who presented with acute noninflammatory diarrhea, and the effectiveness was comparable to that of azithromycin plus loperamide.[199] When given as prophylaxis to travelers, quinolones have produced protection rates ranging from 68% to 92% compared with those in placebo control subjects, but routine use of quinolones or other antimicrobials is not recommended for prevention of diarrhea in travelers.[192,200,201] Contingency treatment at the onset of diarrhea is preferred for travelers, and with this approach, norfloxacin (400 mg twice daily for 3 days)[202] and ciprofloxacin (500 mg single dose)[197] were shown to shorten diarrhea by 1 to 3 days relative to placebo.

In patients with shigellosis, for whom antimicrobials are generally indicated, 5-day courses of norfloxacin, ciprofloxacin, and ofloxacin have been highly effective and generally at least as effective as comparator agents, including ampicillin, TMP-SMX, azithromycin, and ceftriaxone.[192,203] Addition of loperamide to ciprofloxacin may further shorten the duration of diarrhea, but there is risk of clinical worsening and intestinal perforation in this condition.[204] Even a single 750-mg dose of ciprofloxacin may be effective in shigellosis, except those cases caused by *Shigella dysenteriae* type 1, the most virulent of *Shigella* types.[205] Failure rates for ciprofloxacin have increased, however, associated with the emergence of strains resistant to nalidixic acid and ciprofloxacin, particularly in Asia and Africa.[206]

In patients with nontyphoidal *Salmonella* gastroenteritis, symptoms were shortened with ciprofloxacin or norfloxacin in some[207,208] but not all studies.[209] Eradication of stool carriage of *Salmonella* is generally transient,[208,210] but carriage is not necessarily prolonged relative to no treatment.[211] Treatment of *Salmonella* gastroenteritis is generally not indicated, except in immunocompromised and elderly patients because of the risk of invasive disease. In immunocompromised hosts, systemic, nontyphoidal *Salmonella* infections have been successfully treated with ciprofloxacin, but there have been no comparative trials and some relapses have occurred in acquired immunodeficiency syndrome (AIDS) patients.[212]

For *C. jejuni* gastroenteritis, studies of treatment with quinolones have had variable results. Ciprofloxacin (500 mg twice daily for 5 days)[213] and norfloxacin (400 mg twice daily for 5 days)[208] were superior to placebo. Clinical and microbiologic failures have been associated with development of resistant *C. jejuni* in some,[196,214] but not in all, studies using ciprofloxacin.[211] Quinolone resistance in *C. jejuni* has increased. In the 1990s, a CDC survey in selected US counties did not detect ciprofloxacin resistance among a sample of *C. jejuni* isolates from sick people; the resistance rate subsequently rose from 17% in 1997–1999[214a] to 25% in 2012–2014. In a trial done in the years 2000 and 2001 on US military personnel based in Thailand who presented with acute diarrhea, 50% of the *Campylobacter* isolates were resistant to fluoroquinolones, and levofloxacin (500 mg daily for 3 days) was clinically and microbiologically inferior to 1 or 3 days of azithromycin.[215]

For treatment of patients with cholera, norfloxacin (400 mg twice daily for 3 days) was shown to be superior to TMP-SMX, a single dose of doxycycline, and placebo in shortening diarrhea,[216,217] and 3 days of ciprofloxacin (250 mg once daily) and a standard tetracycline (500 mg four times daily) regimen were comparable.[218] A single dose of ciprofloxacin (1 g) or two 500-mg doses of ciprofloxacin has been effective and superior to doxycycline in shortening diarrhea and eradicating *Vibrio cholerae* from stool.[218,219] A single 20-mg/kg dose of ciprofloxacin achieved clinical outcomes similar to, or better than, those achieved with erythromycin (12.5 mg/kg every 6 hours for 3 days).[220] In some areas, such as Bangladesh, however, progressively decreasing susceptibility to ciprofloxacin has been more recently observed along with low efficacy (27%) of single doses of ciprofloxacin.[221,222] In patients with diarrhea caused by *Yersinia enterocolitica, Plesiomonas shigelloides,* and *Aeromonas* spp., quinolones have eradicated the organisms from stool but have not yet been clearly shown to shorten clinical illness.[192]

In studies performed in the late 1980s and early 1990s in patients with enteric fever caused predominantly by *Salmonella enterica* serovar Typhi or serovar Paratyphi, 7-day courses of ciprofloxacin and ofloxacin cured over 90% of patients, shown to be superior to ceftriaxone, with resolution of fever within 5 days.[223] Since the mid-1990s, outbreaks of serovar Typhi strains that were resistant to nalidixic acid (the prototype quinolone that was used for in vitro screening tests) and had reduced susceptibility to fluoroquinolones (ofloxacin MIC of 0.25–1.0 μg/mL) have been reported in a number of countries and in travelers to them.[223,224] Clinical failures and delayed defervescence after short courses (2–3 days) of ofloxacin were more frequent in patients with nalidixic acid–resistant strains versus those with nalidixic acid–susceptible strains.[225–228] Gatifloxacin, which targets both DNA gyrase and topoisomerase IV,

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also failed to meet the expectation to be a better alternative for *Salmonella* infections with increased MICs to fluoroquinolones. Two studies were conducted in Nepal in adults and children with uncomplicated enteric fever. In one, 7 days of gatifloxacin or ofloxacin among 170 patients infected by nalidixic acid–resistant isolates were equally effective.[229] In another study, performed in a background of increasing fluoroquinolone resistance, 7 days of gatifloxacin (10 mg/kg/day) was inferior to ceftriaxone among microbiologically confirmed cases.[230] Chronic fecal carriage of fluoroquinolone-susceptible *S. enterica* serovar Typhi has been eradicated in 83% to 93% of small numbers of patients, including a few with gallstones, given norfloxacin, ciprofloxacin, or ofloxacin for 4 weeks.[223,231,232]

Quinolones are active against *H. pylori* in vitro. Several randomized comparative trials have demonstrated that levofloxacin- and moxifloxacin-based multidrug regimens administered for 7 to 10 days were effective in eradication of *H. pylori.* The eradication rate was approximately 80%, similar to other standard non–fluoroquinolone-containing multidrug regimens.[233–239] The presence of quinolone resistance, however, significantly decreased the eradication rate.[240] Current guidelines recognize that antibiotic resistance should be addressed when choosing treatment regimens for *H. pylori* and do not recommend inclusion of fluoroquinolones in first-line regimens or their repeated use.[241,242]

Data are quite limited on the use of quinolones for treatment of biliary tract infections. In a single small study, 83% of patients with cholecystitis and cholangitis, most associated with *E. coli* bacteremia, responded to intravenous and then oral ciprofloxacin.[243] In patients with biliary stents, late blockage has been thought to be due in part to bacterial adherence to the stent with biofilm formation. In small studies, ciprofloxacin (250 mg PO twice daily) and ofloxacin (200 mg twice daily) were not shown to delay stent blockage.[244,245]

In patients with complicated intraabdominal infections caused by disruption of the integrity of the gastrointestinal tract, a mixture of anaerobes and facultative gram-negative aerobes, with or without enterococci, are usually involved. In a randomized, double-blind trial, ciprofloxacin (400 mg IV every 12 hours/500 mg PO every 12 hours) plus metronidazole (500 mg IV/PO every 6 hours) was compared with imipenem (500 mg every 6 hours) for patients with complicated infections largely caused by disease of the colon, small bowel, and appendix. Ciprofloxacin and metronidazole were given either entirely intravenously or with a switch to oral administration after initial response. Clinical outcomes were similar in all three arms of the study. Regardless of treatment, however, there was a significantly higher rate of treatment failure if enterococci were isolated from the site of infection (28%) than if they were not (14%),[246] suggesting that additional agents active against enterococci should be considered if culture results dictate. Ciprofloxacin plus metronidazole also appeared superior to piperacillin-tazobactam in another double-blind trial, although analysis of treatment failures was incomplete,[247,248] and another study found no differences when ciprofloxacin plus metronidazole was compared with ceftriaxone plus metronidazole.[249]

Moxifloxacin, which has activity against enteric gram-negative bacilli similar to that of ciprofloxacin and additional activity against anaerobic bacteria, was studied in double-blind randomized trials as a single agent (400 mg IV/PO once daily) in comparison to piperacillin-tazobactam (3.75 g IV every 6 hours) followed by amoxicillin-clavulanate (914 mg PO every 12 hours), both regimens given for up to 14 days,[250] and in comparison to ceftriaxone (2 g IV once daily) plus metronidazole (500 mg IV twice daily) given for 3 to 14 days.[251] In the first study, clinical cure rates were 80% and 78% in the two arms, respectively. In the second study, although clinical response rates for moxifloxacin met the noninferiority criteria, they were significantly lower than in the ceftriaxone-metronidazole arm (90.2% vs. 96.5%).[251] The high rates of response in both studies would be expected because of the low overall Acute Physiology and Chronic Health Evaluation (APACHE) II scores of the enrolled patients. High rates of susceptibility to moxifloxacin among baseline anaerobic isolates (87%) were found overall in these and related moxifloxacin intraabdominal infection trials.[252] Current IDSA guidelines for intraabdominal infections include moxifloxacin alone and combinations of either ciprofloxacin or levofloxacin with metronidazole among recommended regimens for initial therapy.[253]

Use of quinolones in peritonitis has been evaluated most in patients undergoing chronic ambulatory peritoneal dialysis (CAPD) and in patients with cirrhosis. Oral ofloxacin, 300 mg once daily, and ciprofloxacin, 500 mg once daily, have cured episodes of peritonitis in CAPD patients, but failures in infections caused by the common coagulase-negative staphylococci have occurred. Higher concentrations of ciprofloxacin have been achieved by adding drug to the dialysate (20–50 μg/mL), with outcomes similar to those with standard regimens of intraperitoneal vancomycin plus gentamicin.[254] Oral regimens may have been less effective due to binding of fluoroquinolones to oral phosphate binders, which reduce their bioavailability. A combination of intraperitoneal ciprofloxacin (50 mg/L) and rifampin (50 mg/L) produced a 65% cure rate, which was superior to that with intraperitoneal cephradine.[255] When intraperitoneal vancomycin was used, oral levofloxacin was inferior to an intraperitoneal aminoglycoside in patients with gram-negative CAPD infections, a limitation that appeared to be related to the prevalence of levofloxacin resistance in these organisms.[256] Current International Society for Peritoneal Dialysis guidelines recommend oral treatment for peritonitis due to susceptible bacteria with the following quinolones: ciprofloxacin (250 mg twice daily), levofloxacin (250 mg once daily), moxifloxacin (400 mg once daily), and intraperitoneal administration of ciprofloxacin or ofloxacin.[257]

In treatment of spontaneous bacterial peritonitis in cirrhotic patients, ciprofloxacin has been compared with cefotaxime, ceftriaxone, or ceftazidime; ofloxacin has been compared with cefotaxime; and moxifloxacin has been compared with amoxicillin-clavulanate.[258] With 35 to 123 patients in these studies, no differences in clinical outcomes were found. In patients with cirrhosis at high risk for recurrent spontaneous bacterial peritonitis, norfloxacin, 400 mg once daily given as prophylaxis, reduced recurrences by threefold.[259] Norfloxacin and ciprofloxacin were also studied for up to 1 year for the primary prophylaxis of spontaneous bacterial peritonitis among high-risk patients with low ascitic protein concentration.[260–264] A trend toward a reduced number of episodes of peritonitis was observed in all studies, and in a few, a notable increased probability of survival was also found. Prolonged use of norfloxacin was, however, later associated with increasing occurrence of quinolone-resistant bacteria[263,265]; in this respect, it is interesting that the survival advantage was substantial at 3 months (94% vs. 62%; $P = .003$) but only 60% versus 48% by 1 year ($P = .05$).[261] Patients who have been on this prophylaxis and develop peritonitis should be treated with agents other than a fluoroquinolone because the risk of quinolone resistance is high in this group.[266] Similarly, primary prophylaxis had also been recommended for patients with cirrhosis and gastrointestinal bleeding because in several studies, performed in the 1990s, that tested mainly quinolones, prophylaxis was efficacious in reducing the number of deaths and bacterial infections.[267] In a more recent study,[261] however, oral norfloxacin and intravenous ceftriaxone were compared for prophylaxis in 111 cirrhotic patients with gastrointestinal bleeding. Spontaneous bacteremia or bacterial peritonitis was significantly higher in patients receiving norfloxacin.[268] Thus the risks of selecting resistant enteric bacteria must also be considered before embarking on prolonged use of quinolones in prophylaxis.

Respiratory Tract Infections

A range of respiratory tract pathogens is susceptible to a number of quinolones in vitro. *Haemophilus influenzae, M. catarrhalis,* and many enteric gram-negative bacilli, as well as the agents of atypical pneumonias—*M. pneumoniae, C. pneumoniae,* and *L. pneumophila*—are generally susceptible to systemic quinolones, such as ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and delafloxacin. High intracellular concentrations of quinolones are likely advantageous for intracellular pathogens, such as *L. pneumophila* and *M. tuberculosis.* Levofloxacin, moxifloxacin, gemifloxacin, and delafloxacin have improved activity against *S. pneumoniae* and have been referred to as respiratory quinolones.

Patients with acute bacterial exacerbations of chronic bronchitis have been treated with many different quinolones, which have generally been effective in eradicating *H. influenzae* from sputum.[269] In studies with ciprofloxacin, eradication rates for *S. pneumoniae* and *P. aeruginosa* were lower, and some failures have been associated with the development

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of bacterial resistance. In comparative trials with respiratory quinolones, however, clinical responses have usually been similar to or better than those with ampicillin, amoxicillin, cefaclor, and macrolides.[270] Clinical and microbiologic outcomes were similar for levofloxacin (500 mg once daily) versus cefuroxime axetil[271–273]; moxifloxacin (400 mg once daily) versus clarithromycin,[274,275] azithromycin,[276,277] levofloxacin,[278] or a new quinolone, zabofloxacin[279]; and gemifloxacin (320 mg once daily) versus clarithromycin[280] or levofloxacin.[281] Five- or 7-day courses seemed to be sufficient, with clinical response rates of 85% to 95%, and 5- and 10-day courses of moxifloxacin were comparable to each other (94% responses).[275]

Moxifloxacin and gemifloxacin were superior to clarithromycin in eradicating *H. influenzae* from sputum, probably because of the lesser activity of clarithromycin against this organism.[274,278] In a double-blind, randomized study of patients with acute exacerbations of chronic bronchitis, characterized by dypsnea and increased volume of purulent sputum, moxifloxacin (400 mg once daily for 5 days) was superior to standard therapies (7 days of amoxicillin, 500 mg three times daily; clarithromycin, 500 mg twice daily; or cefuroxime axetil, 250 mg twice daily) in clinical cure and bacteriologic eradication.[282] In a study of more severely ill, hospitalized patients with acute exacerbations of chronic bronchitis, gemifloxacin (320 mg PO once daily for 5 days) had better clinical responses in the intent-to-treat analysis and a shorter time to hospital discharge relative to ceftriaxone (1 g IV once daily for ≤3 days), followed by cefuroxime axetil (500 mg PO twice daily for ≤7 days).[283] Time to next recurrent exacerbation was lengthened after treatment with ciprofloxacin versus clarithromycin[284] but was comparable to that after treatment with cefuroxime axetil,[285] and average infection-free intervals were similar in both comparisons. Moxifloxacin treatment was associated with a significant 13% to 27% increase in the time to next exacerbation relative to conventional therapies with amoxicillin, clarithromycin, or cefuroxime,[282] and the proportion of patients without a recurrence after treatment of an exacerbation with gemifloxacin was significantly lower than that after treatment with clarithromycin (71% vs. 58%, respectively, at 26 weeks).[280] Repeated courses of moxifloxacin (5 days every month) in patients with stable chronic obstructive pulmonary disease were, however, similar to placebo in reduction in bacterial load, and had more treatment-related adverse events.[286]

In patients with community-acquired pneumonias, ciprofloxacin and ofloxacin have consistently eradicated *H. influenzae* and *M. catarrhalis*.[79] Although cures of pneumococcal pneumonias, including a few cases with bacteremia, have been reported with intravenous and then oral ciprofloxacin[287] and ofloxacin[288,289] and with oral ofloxacin alone,[290] failures with both drugs have occurred, and pneumococcal bacteremia has developed during ciprofloxacin therapy of pneumonia.[143] For this reason, ciprofloxacin is generally not used to treat lower respiratory infections, with the exception that it is recommended as part of a combination regimen for treatment of inhalational anthrax (see "Skin and Soft Tissue Infections"). For respiratory quinolones with greater pneumococcal activity, similar or better clinical and microbiologic efficacies have been found for levofloxacin (500 mg IV/PO once daily) versus ceftriaxone (with or without erythromycin), followed by cefuroxime axetil,[291] ceftriaxone alone,[292] amoxicillin-clavulanate alone or together with clarithromycin, and solithromycin or tigecycline.[293–296] Five days of a higher-dose regimen of levofloxacin (750 mg once daily) was comparable in clinical success to 10 days of the lower dose (500 mg once daily),[297] with a higher proportion of patients with resolution of fever and purulent sputum by day 3.[298] Comparable outcomes with generally high cure rates have also been seen in comparisons of moxifloxacin (400 mg PO once daily) versus clarithromycin,[299] ceftriaxone plus levofloxacin,[300] solithromycin (PO and IV-to-PO),[301,302] or amoxicillin[303] and comparisons of gemifloxacin (320 mg PO once daily) versus ceftriaxone, followed by cefuroxime axetil,[304] or versus amoxicillin-clavulanate.[305] A 5-day course of gemifloxacin also appeared to be comparable to a 7-day course.[306]

In addition to the initial study with levofloxacin,[291] a few studies, including one with moxifloxacin[307] and another with gemifloxacin,[308] have also demonstrated superiority relative to the comparator agents in treatment of patients with community-acquired pneumonia. In hospitalized patients requiring initial parenteral therapy, moxifloxacin (400 mg IV/PO once daily) was superior to amoxicillin-clavulanate (IV/PO) with or without clarithromycin, with more rapid defervescence, higher rates of clinical success (93% vs. 85%), and higher rates of bacterial eradication from sputum (94% vs. 82%).[307] For hospitalized patients older than 65 years, moxifloxacin (400 mg IV/PO once daily) produced a trend toward slightly better overall clinical outcomes than levofloxacin (500 mg IV/PO once daily), with a higher proportion of patients with clinical recovery by days 3 to 5.[309] No studies have compared moxifloxacin with the higher dose of levofloxacin. Gemifloxacin (320 mg PO once daily) produced modestly better clinical success in comparison to trovafloxacin (200 mg PO once daily) in an intent-to-treat analysis (88% vs. 81%), with similar responses in the per-protocol analysis (96% vs. 94%).[308]

Clinical responses in the subgroups of patients (usually numbering 10–20 patients) with pneumococci isolated from sputum from various trials were usually similar to the overall response rates (levofloxacin, 81%–100%[292]; moxifloxacin, 100%[299,307]; and gemifloxacin 90%–100%).[304,308] Most studies have included patients with mild-to-moderate pneumonia, but those with levofloxacin and gemifloxacin[304] included patients with severe pneumonia by using clinical criteria similar to those used for stratification of risk of death,[310] with 91% and 87% clinical cures, respectively. Outcomes in patients with pneumococcal bacteremia and pneumonia, a more severe test of drug efficacy, were good overall with levofloxacin (91%, 107 of 117 cured),[291,311] moxifloxacin (88%, 21 of 24 cured; and 70%, 7 of 10 cured),[301,302,307,312] and gemifloxacin (100%, 12 of 12 cured).[304] Clinical failures associated with prior or acquired quinolone resistance in pneumococci have been reported with levofloxacin therapy but have not yet been reported in association with the less extensive use of moxifloxacin or gemifloxacin.[313] In light of the high selection pressure for resistance imposed by broad-spectrum combination therapy for community-acquired pneumonia, a recent study from the Netherlands evaluated the paradigm of combining β-lactams with fluoroquinolones or macrolides.[314] The mortality difference between the β-lactam strategy and the fluoroquinolone strategy was in favor of the fluoroquinolone strategy, but was not statistically significant, and no differences were found in other secondary outcomes.

In aspiration pneumonia and lung abscess, coverage for oral anaerobic bacteria is generally important. Moxifloxacin, relative to other fluoroquinolones, exhibits enhanced activity in vitro against anaerobic bacteria and, at 400 mg intravenously/orally once daily, produced similar clinical responses compared with ampicillin-sulbactam (2 g/1 g IV three times daily), followed by sultamicillin (750 mg PO twice daily), in treatment of patients with aspiration pneumonia (32 of 48 [67%] in both groups) or lung abscess (15 of 19 [79%] vs. 11 of 15 [73%]).[315]

Among atypical pneumonias, smaller numbers of patients with pneumonias caused by *Legionella,*[316,317] *Mycoplasma,*[79] and *C. pneumoniae*[318] have also responded to ciprofloxacin and ofloxacin, but some apparent failures were seen in patients with *M. pneumoniae* and *C. pneumoniae* infection treated with ofloxacin.[289] Clinical responses to levofloxacin,[291] moxifloxacin,[307,319] and gemifloxacin[304,306,310] in usually small numbers (except for the larger number in the trial of gemifloxacin[310]) of patients with *C. pneumoniae, M. pneumoniae,* and *L. pneumophila* infection, usually diagnosed serologically, have generally been high. In observational studies, patients with *Legionella* pneumonia had similar or better clinical responses to levofloxacin relative to macrolides.[320,321] With pneumonia caused by other atypical pathogens—particularly with *M. pneumoniae* infections, which may improve without treatment—assessment of responses is difficult because study designs often do not compare the rapidity of symptomatic improvement between active and inactive agents. Respiratory quinolones appear to be at least as good as if not superior to macrolides for treatment of *Legionella* pneumonia.[322]

Hospital-acquired pneumonias, which are commonly caused by gram-negative bacilli, have responded to intravenous ciprofloxacin[143,323] and ofloxacin,[288] and responses to ciprofloxacin correlated with the level of susceptibility of the infecting organism, with better bacteriologic responses in infections caused by *Haemophilus* spp. and members of the Enterobacteriaceae than in infections caused by the less susceptible *P. aeruginosa*. Comparative trials of imipenem versus ciprofloxacin[324]

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or levofloxacin[325] for treatment of patients with nosocomial pneumonia have been published. For hospitalized patients with severe pneumonia, ciprofloxacin in high dose (400 mg IV every 8 hours) was compared with imipenem (1000 mg IV every 8 hours) in a multicenter, randomized, double-blind trial.[324] Most of the patients had nosocomial pneumonia (78%) and were mechanically ventilated (79%). Clinical and microbiologic response rates were somewhat higher in the ciprofloxacin (69% and 69%, respectively) than the imipenem (56% and 59%, respectively) group, and bacterial eradication rates were highest for members of the Enterobacteriaceae. Substantially poorer responses in both treatment groups were seen in patients with *P. aeruginosa* infection, and for both *P. aeruginosa* and *S. aureus,* persistence in sputum was substantial (60% to 67% and 35% of patients, respectively) and was associated with development of resistance. For these reasons, combination therapy and use of maximum approved doses of ciprofloxacin (750 mg PO or 400 mg IV every 8–12 hours) may be preferred when ciprofloxacin is used in patients with *P. aeruginosa* infection. Addition of ciprofloxacin to meropenem did not provide additional clinical benefit over meropenem alone overall in patients with ventilator-associated pneumonia, but in the subset of patients with *P. aeruginosa, Acinetobacter* spp., or multidrug-resistant gram-negative bacilli, bacteriologic eradication was higher in the combination therapy group.[326] In a multicenter, randomized, open-label trial, high-dose levofloxacin (750 mg IV/PO) produced clinical responses similar to those with imipenem (500 mg to 1 g every 6–12 hours), followed by ciprofloxacin (750 mg PO every 12 hours), when both regimens were given for 7 to 15 days (135 of 204 patients [66%] vs. 143 of 206 patients [69%] in intent-to-treat analysis), including a severely ill subset of patients with APACHE II scores less than 20 (mean APACHE II scores were 15.0 vs. 14.8).[325] A later analysis of the subgroup of patients with ventilator-associated pneumonia also found similar efficacy in the two treatment groups.[327] Patients also received additional therapy if they had documented infection with methicillin-resistant *S. aureus* (vancomycin for both study arms) or *P. aeruginosa* (ceftazidime for levofloxacin arm and amikacin for imipenem arm). Microbiologic eradication rates were also similar overall. In patients with *P. aeruginosa* infection, however, there was a trend toward better clinical and microbiologic responses in the levofloxacin arm, suggesting that levofloxacin plus ceftazidime might be somewhat better than imipenem plus amikacin for these infections. No data were included about emergence of bacterial resistance in this study, but prior exposure to levofloxacin has been associated with the emergence of resistance in *P. aeruginosa*.[328] Recent IDSA guidelines for the treatment of hospital-acquired and ventilator-associated pneumonia have limited the role of combination therapy to the setting of definite therapy of infection with *P. aeruginosa* in patients who remain in septic shock or at a high risk for death.[329]

There has been a single reported study of moxifloxacin (400 mg IV/PO once daily) in treatment of hospital-acquired pneumonia in patients who were screened to exclude clinical risk factors for resistant pathogens. The study was terminated early because of slow enrollment and had identified no differences in outcomes relative to ceftriaxone, followed by cefuroxime.[330]

Mild-to-moderate respiratory exacerbations in patients with cystic fibrosis and *P. aeruginosa* in sputum responded clinically to oral ciprofloxacin (750 mg twice daily) and ofloxacin (400 mg twice daily), and similarly to conventional parenteral therapies that use an antipseudomonal β-lactam and tobramycin.[143] In patients with more severe exacerbations, however, conventional parenteral combination therapy may be superior. Rarely is *P. aeruginosa* eliminated from sputum by any regimen in patients with cystic fibrosis. Rotating the use of different regimens may reduce the selective pressure for persistence of resistant bacteria that may emerge with either type of regimen. Levofloxacin inhalation solution is an aerosolized fluoroquinolone licensed for treatment and maintenance therapy in patients with cystic fibrosis and chronic *P. aeruginosa* lung infections. In a randomized noninferiority study, levofloxacin inhalation solution (three 28-day on/off cycles) was noninferior to the same regimen with inhalational tobramycin. Levofloxacin inhalation solution was well tolerated, with dysgeusia (distorted taste) as the most frequent adverse event; a greater than fourfold increase in MIC of levofloxacin was observed in 21% of the *P. aeruginosa* isolates, similar to the comparator group.[331]

Acute purulent sinusitis acquired in the community is often caused by a similar group of pathogens to those that cause acute bacterial exacerbations of chronic bronchitis and may be seen as a complication of viral upper respiratory infections. Anaerobic bacteria are usually present in only a small percentage of patients and are more likely if sinusitis is chronic or associated with dental infections. Establishment of drainage of the infected sinus cavity by use of nasal decongestants or other means is an important adjunctive therapy in addition to antimicrobial agents. There are a number of trials comparing quinolones with other therapies in patients with acute purulent sinusitis, including ciprofloxacin (500 mg PO twice daily) versus cefuroxime axetil,[331a] levofloxacin (500 mg PO once daily) versus amoxicillin-clavulanate[331b] or clarithromycin,[331c] and moxifloxacin (400 mg PO once daily) versus cefuroxime axetil[331d,332] or amoxicillin-clavulanate.[331e] In all of these studies, there were comparable clinical responses between the quinolone and its comparator, with generally high response rates (87% to 96%). A 5-day course of levofloxacin at the higher dose (750 mg once daily) was also comparable to a 10-day course at the lower dose (500 mg once daily).[331f] In these or other studies in which microbiologic samples were obtained by sinus puncture or nasal endoscopy before therapy, *H. influenzae* and *S. pneumoniae* were the predominant pathogens, and clinical responses in the subset of patients from whom *S. pneumoniae* was isolated were high: 100% for levofloxacin[331f] and 97% for moxifloxacin.[332] Thus these quinolones may be an alternative to, but offer no advantage over, nonquinolone therapies for treatment of acute community-acquired purulent sinusitis. A prospective, multicenter, randomized, double-blind trial compared the efficacy and safety of moxifloxacin (400 mg daily for 5 days) versus placebo in the treatment of culture-positive acute bacterial rhinosinusitis.[333] Interestingly, moxifloxacin was not significantly superior to placebo for the primary end point.

Although acute otitis media is caused by pathogens similar to those that cause acute bacterial sinusitis, fluoroquinolones have not been widely used because acute otitis media is usually a disease of children, in whom joint toxicity of fluoroquinolones had been a concern. Invasive otitis externa in diabetics is usually caused by *P. aeruginosa* and may respond to oral ciprofloxacin (750 mg twice daily) given for 6 weeks.[334,335] No studies comparing quinolones with conventional parenteral therapies in adults have been reported.

Bone and Joint Infections

The prolonged antimicrobial therapy usually given for bone and joint infections is facilitated by effective oral agents, and quinolones may fill this role in some cases.[336] For treatment of chronic osteomyelitis, there have been noncomparative trials using ciprofloxacin, ofloxacin, pefloxacin, or levofloxacin, in which treatment was usually for 6 or more weeks and follow-up was for at least 6 months after completion of therapy.[79,143,337,338] Clinical cures after oral ciprofloxacin (750 mg twice daily) were 75% overall in infections in which gram-negative bacilli predominated, and similar rates of cure were reported in the smaller subgroups of patients with *P. aeruginosa* and methicillin-susceptible *S. aureus* (MSSA) infections. Failures were associated with incomplete débridement, the presence of foreign bodies, and the development of resistance in *P. aeruginosa, S. aureus,* and *Serratia marcescens*. Levofloxacin (500 mg once daily) was effective in 9 of 15 patients (60%), with largely polymicrobial (*S. aureus* in 7 and *P. aeruginosa* in 3; all but 3 had other organisms as well) infections; in 4 cases, failures were thought to be due to inadequate débridement.[337] Three months of treatment with ciprofloxacin produced a cure rate of 60% in one study of osteomyelitis in the feet of diabetics[339]; ofloxacin produced a similar response rate.[340] Calcaneal osteochondritis caused by nail puncture wounds of the foot is often due to *P. aeruginosa*. Local débridement in combination with ciprofloxacin (400 mg IV every 12 hours, then 750 mg PO twice daily) given for 14 days appears to be highly effective for this condition, with cures in all 18 patients with *P. aeruginosa* infection and in 2 with *S. aureus* infection.[341]

In four small comparative trials, ciprofloxacin (750 mg twice daily) and ofloxacin (400 mg twice daily) have generally produced apparent rates of cure similar to those of conventional parenteral therapies using β-lactams with or without an aminoglycoside,[143,342] but the power of

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these studies to detect differences between the regimens was small. For ofloxacin, cures of MSSA infections were 80% (10 of 12), but cures of *P. aeruginosa* infections were only 25% (1 of 4).[342] For patients with spinal brucellosis, ciprofloxacin (500 mg PO twice daily) plus rifampin (600 mg PO once daily) produced cure rates similar to doxycycline plus streptomycin given for 12 to 24 weeks when compared in consecutive, nonrandomized groups.[343] Randomized, controlled studies do not, however, provide support for the use of quinolone-based combinations as a first-line therapy, and quinolone-based regimens were associated with a higher relapse rate than comparators.[344]

For septic arthritis of prosthetic joints, standard therapy involves staged prosthesis removal and débridement, prolonged antibiotic treatment, and prosthesis reimplantation. Infections of prosthetic joints caused by *S. aureus* and coagulase-negative staphylococci have been treated with ofloxacin (200 mg PO three times daily) plus rifampin (900 mg once daily) for 6 to 9 months using the standard approach as well as débridement with retention of the prosthesis in patients for whom removal was not possible.[345] With prolonged follow-up after completion of therapy, response rates were high in patients after the standard approach (81%–93%) and unexpectedly high in the patients with retained prostheses (54%–70%). Similar results have been reported for ciprofloxacin plus rifampin that also document the importance of rifampin in the antimicrobial regimen, because failure rates were high when ciprofloxacin was used alone.[346] Ceftazidime (1.5 g every 12 hours) given for 6 weeks plus ciprofloxacin (500 mg PO every 8 hours) given for 6 months also appeared to cure *P. aeruginosa*–infected orthopedic implants without prosthesis removal.[347] Patients with infections of prosthetic joints caused primarily by staphylococci have also been successfully treated with a combination of levofloxacin (500 mg PO once daily) and rifampin (600 mg once daily) given for extended periods after débridement with prosthesis retention.[348,349] A randomized comparison of short (8 weeks) and long (3–6 months) durations of treatment with levofloxacin at a higher dose (750 mg PO once daily) and rifampin (600 mg daily) found that at a median of 540 days of follow-up, the short course was no worse than the long course in 63 patients with staphylococcal prosthetic joint infection after débridement and prosthesis retention (73% vs. 58% cure in intent-to-treat analysis and 92% vs. 95% in per-protocol analysis for short and long durations, respectively).[350] For patients with rigid internal fixation devices (plates and screws) infected by staphylococci that were débrided and retained, a levofloxacin-rifampin regimen resulted in an overall cure rate of 72%.[351] For patients with either prostheses or internal fixation devices, failures were associated with a longer duration of symptoms before débridement.[348,351] Thus, for salvage of some patients in whom orthopedic devices cannot be removed, early débridement and extended treatment with a combination of a fluoroquinolone and rifampin (or ceftazidime) could be considered if the infecting organism is susceptible to both agents in the combination.

There are few other data on treatment of septic arthritis with quinolones, most often with ciprofloxacin or ofloxacin.[79] Infections caused by *N. gonorrhoeae* and *E. coli* have responded to oral therapy. Failures have been seen in infections of prosthetic joints and infections caused by *S. aureus* and *P. aeruginosa* infections.

Skin and Soft Tissue Infections

Although the most common causes of cellulitis and pyodermas are streptococci and *S. aureus,* in patients with diabetes and peripheral vascular disease, decubitus ulcers, and some surgical wound infections, soft tissues may become infected with a mixture of bacteria that includes, in addition to streptococci and staphylococci, aerobic gram-negative bacteria and anaerobes. Quinolones have been evaluated as treatment for skin and soft tissue infections in some of these subgroups of patients.[352,353]

For uncomplicated skin infections, comparable clinical response rates (usually 90% or higher in both arms) have been reported for ofloxacin (400 mg PO twice daily) versus cephalexin (500 mg four times daily),[354] levofloxacin (500 mg PO once daily) versus ciprofloxacin (500 mg PO twice daily),[355] and moxifloxacin (400 mg PO once daily) versus cephalexin (500 mg three times daily).[356] *Staphylococcus aureus* and *Streptococcus pyogenes* were the dominant pathogens in these studies, but methicillin-resistant *S. aureus* (MRSA) strains, which are commonly also resistant to quinolones, were infrequently reported. Levofloxacin was significantly better than ciprofloxacin in eradicating *S. aureus* in one study.[355] In these and noncomparative studies,[79] failures have been seen with infections caused by *P. aeruginosa* (11%), streptococci (6%), and *S. aureus* (5%) and have been associated with the development of resistant organisms, which for *P. aeruginosa* may be more frequent in diabetic patients.[354]

For complicated skin infections, comparisons of oral ciprofloxacin (750 mg twice daily)[357,358] and ofloxacin (400 mg twice daily)[359] with intravenous cefotaxime or ceftazidime, given for 9 to 12 days to patients with mixed infections in which gram-negative bacilli predominated, showed similar rates of clinical and bacteriologic efficacy, in the range of 79% to 98% clinical cures. *Staphylococcus aureus* and *P. aeruginosa* were the most common pathogens in these studies, with few MRSA strains identified. Levofloxacin (750 mg IV/PO once daily) compared with ticarcillin-clavulanate (3.1 g IV every 4 to 6 hours), followed by amoxicillin-clavulanate (875 mg PO every 12 hours), produced similar overall clinical success (116 of 138 patients [84%] vs. 106 of 132 patients [80%]).[360] Levofloxacin was superior in eradicating MSSA, the dominant pathogen, and similar in eradicating a mix of gram-negative pathogens. The subgroup with diabetic foot infections was too small to assess adequately. In diabetic foot infections without osteomyelitis, the overall rate for complete healing using ciprofloxacin alone was 50%.[339] The polymicrobial nature of these infections, which may include anaerobes, may be a limiting factor for efficacy of some fluoroquinolones. Use of additional antimicrobial agents with activity against anaerobes should be considered in these patients. In a double-blind, randomized trial, moxifloxacin (400 mg IV/PO once daily) produced comparable clinical responses and bacterial eradication rates relative to piperacillin-tazobactam (3.375 g IV every 6 hours), followed by amoxicillin-clavulanate, in patients with dominant cellulitis or skin abscess.[361] In the subgroups of patients in whom *S. aureus* (only a minority were MRSA), *S. pyogenes,* and enteric gram-negative bacteria were isolated and in the subgroup of diabetic foot infections, clinical response rates were also similar. In a randomized, double-blind trial, delafloxacin (300 mg IV) was compared to linezolid (600 mg IV) and vancomycin (15 mg/kg IV) each given twice daily in 256 patients with acute bacterial skin and skin structure infections.[362] *Staphylococcus aureus* was the dominant pathogen identified, with MRSA exceeding MSSA, and cellulitis (~45%) and major abscess (~28%) were the dominant infection types. Delafloxacin was significantly better than vancomycin in clinical cure (57 of 81 patients [70%] vs. 53 of 98 patients [54%]) and in reduction of local erythema, with no significant differences between delafloxacin and linezolid. In a phase 3, double-blind, randomized trial, delafloxacin was also shown to be noninferior to vancomycin plus aztreonam, with similar objective reductions in erythema (78% vs. 81%), rates of clinical cure (70% vs. 67%), and eradication of MRSA (100% vs. 98%).[363]

The role of quinolones in the treatment of cutaneous and other forms of anthrax received considerable attention as a result of bioterrorism cases of anthrax in the United States in 2001. Activity in vitro is excellent for a number of fluoroquinolones, and ciprofloxacin (500 mg PO twice daily) is the recommended regimen for cutaneous disease and prophylaxis after exposure to anthrax spores.[364] Inhalational anthrax is treated with intravenous ciprofloxacin in combination with other agents.

For patients with uncomplicated cellulitis or pyodermas, in whom streptococci and staphylococci are the most likely pathogens, respectively, conventional therapies with penicillin, semisynthetic penicillins, and cephalosporins, either oral or parenteral, remain the therapy of choice. For infections with MRSA, for which the quinolones were initially hoped to be valuable oral therapies, rapid emergence of quinolone resistance has become a particular problem, and resistance is now highly prevalent in many medical centers.[365,366] In addition, with the increasing frequency of MRSA as a cause of skin infections in the community and the emergence of fluoroquinolone resistance in community strains (along with established resistance in hospital strains),[367] fluoroquinolones cannot be relied on overall for empirical therapy of serious skin infections possibly caused by staphylococci. The exception appears to be delafloxacin, which has in vitro activity against MRSA, and for which efficacy has been shown in MRSA skin infections in initial clinical trials. It remains important to confirm the proper choice of antimicrobial by

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isolation and susceptibility testing of the relevant pathogen when possible.

Other Uses

Because of resistance to conventional antituberculosis agents, quinolones are being used for treatment of mycobacterial infections.[368] In patients with multidrug-resistant pulmonary tuberculosis, ofloxacin (300 or 800 mg once daily) has been used in combination with other second-line agents, with sputum conversions and apparent clinical cures,[369] but in cases in which ofloxacin was the only active drug, there was failure of sputum conversion and development of ofloxacin resistance.[369,370] Ciprofloxacin (750 mg PO once daily) is less effective in combination regimens than are other first-line agents.[371,372] Levofloxacin and moxifloxacin, however, are being used in second-line regimens for treatment of multidrug-resistant tuberculosis. For early bactericidal activity against *M. tuberculosis* in sputum, levofloxacin (1 g once daily) and moxifloxacin (400 mg once daily) were similar to isoniazid (300 mg once daily).[373] Moxifloxacin (400 mg) was comparable to ethambutol as the fourth component of a regimen of isoniazid, rifampin, and pyrazinamide for sputum conversion within the first 2 months of therapy, with no difference between dosing 5 days per week versus 3 days per week, after the first 2 weeks of daily therapy.[374] A later study, however, in which almost all patients had lung cavities found that moxifloxacin versus ethambutol, in a four-drug regimen, was associated with accelerated reduction in viable bacilli in sputum when adjusted for patient factors that affect rate of sputum conversion.[375] Three recent randomized controlled trials compared standard 6-month regimens with quinolone-containing 4-month regimens in the treatment of rifampin-sensitive pulmonary tuberculosis, but all three studies failed to show noninferiority of the quinolone-containing regimen.[376–378] Somewhat surprisingly, in extensively drug-resistant tuberculosis, which by definition includes resistance to quinolones, the presence of moxifloxacin in the treatment regimen was associated with 40% higher favorable outcomes in a meta-analysis.[379]

Because of widespread quinolone use for respiratory and other indications, there have been concerns about selection of resistance and masking of symptoms in undiagnosed tuberculosis patients, particularly in areas of high endemicity. Prior quinolone exposure for longer than 10 days has been associated with a sevenfold increased risk of quinolone resistance in *M. tuberculosis* isolates and a 17-fold increased risk if the exposure was greater than 60 days before the diagnosis of tuberculosis.[380] In a randomized trial of patients in Hong Kong with community-acquired pneumonia or exacerbations of bronchiectasis, 4.8% of those treated with amoxicillin-clavulanate were diagnosed with active tuberculosis within 12 months, in contrast to 2.4% of those treated with moxifloxacin for 5 days and 0% of those treated for 10 days, suggesting potential masking by moxifloxacin.[381] In an open-label, randomized controlled trial of patients with tuberculous meningitis, a levofloxacin-containing (10 mg/kg up to 500 mg) regimen produced better survival that a rifampin-containing (10 mg/kg up to 450 mg) regimen, both in combination with isoniazid, pyrazinamide, ethambutol, and prednisolone, but the levofloxacin-containing regimen was associated with significantly more seizures and myoclonus.[382] In a subsequent study, however, addition of levofloxacin to a standard four-drug regimen containing rifampin did not result in improved outcomes and was also associated with an increased occurrence of seizures.[383]

For nontuberculous mycobacteria, ciprofloxacin (750 mg twice daily or 500 mg three times daily) has been used in three-drug (clarithromycin plus amikacin)[384] and four-drug (rifampin, ethambutol, and clofazimine)[385] regimens in patients with AIDS and *M. avium-intracellulare* complex bacteremia. Improvement in symptoms occurred with both regimens, but clearance of bacteremia appeared better with the clarithromycin-containing three-drug regimen.[386] In cutaneous *M. fortuitum* infections, ciprofloxacin used alone was followed by relapse and the development of drug resistance,[143] but ofloxacin has been used successfully in some sternotomy infections caused by this pathogen.[387] With agents used against *M. leprae,* there have been reports of clinical improvement in patients with lepromatous leprosy given ofloxacin (400 mg once daily) and pefloxacin (800 mg once daily),[388] and in a randomized, double-blind study of patients with paucibacillary leprosy, at 10 years follow-up, ofloxacin (400 mg once daily) plus rifampin (600 mg once daily) given for 28 days produced clinical improvements comparable to dapsone (100 mg once daily) plus rifampin (600 mg every month) given for 6 months.[389]

For patients with bacteremias, intravenous ciprofloxacin and ofloxacin have been effective in cases caused by enteric gram-negative bacilli, although responses have been poor for *P. aeruginosa* bacteremias when these drugs were used in relatively low doses of 200 mg twice daily.[390,391] In neutropenic patients with fever, ciprofloxacin in combination with aminoglycosides produced defervescence and cure of documented infections comparable to standard β-lactam–aminoglycoside combinations,[392] but ciprofloxacin monotherapy was less effective than such combinations[393] and should not be used. Although lower doses were used in earlier studies, more recent studies have used regimens of ciprofloxacin (400 mg IV every 8 hours; in one case, followed by 750 mg PO twice daily), either alone[394] or in combination with piperacillin.[395] Ciprofloxacin alone was comparable to ceftazidime plus amikacin, and ciprofloxacin plus piperacillin was comparable to tobramycin plus piperacillin in resolution of fever, but changes in therapy were necessary in more than half of patients in both arms of both studies. Use of quinolones in this setting should be cautious and should be considered principally as an alternative regimen when there are reasons for not choosing standard regimens with combinations of β-lactams and aminoglycosides.

There has been an increase in interest in defining low-risk groups of neutropenic patients who might be safe candidates for oral antimicrobial therapy for fever because of the potential for increased convenience and reduced costs. Quinolones have been components of such oral regimens.[396,397] These trials evaluated a combination of oral ciprofloxacin and amoxicillin-clavulanate compared with intravenous ceftazidime in one trial[397] and with intravenous ceftriaxone plus amikacin in the other.[396] The trials involved patients with fever and neutropenia from cancer chemotherapy and who were able to take oral medications and were considered to have low risk of serious complications, based on the absence of other diseases and documented infection and a projected duration of neutropenia of less than 10 days. Success of treatment in patients given the oral and parenteral regimens was similar in both studies, although the oral regimen was associated unexpectedly with a higher incidence of adverse effects (16% vs. 1%, respectively), largely nausea and vomiting.[397] Renal failure reported in an earlier trial of ciprofloxacin plus clindamycin for treatment of a similar group of patients was not seen in these trials.[398] In a double-blind, randomized trial, moxifloxacin (400 mg PO daily) alone was similar to ciprofloxacin (750 mg twice daily) plus amoxicillin-clavulanate in clinical response (80% vs. 82%).[399] Guidelines of the IDSA recommend that febrile neutropenic patients with low risk, defined as anticipated neutropenia for less than or equal to 7 days and no or few comorbidities, are candidates for oral therapy with a regimen of ciprofloxacin or levofloxacin plus amoxicillin-clavulanate.[400]

Oral ciprofloxacin (500 mg twice daily), ofloxacin (300 mg twice daily), and norfloxacin (400 mg twice daily), given as prophylaxis in neutropenic patients, have consistently reduced the occurrence of gram-negative bacteremia and, in some cases, prolonged the time to first fever, but breakthrough gram-positive bacteremias have occurred, particularly streptococcal bacteremias in bone marrow transplant recipients.[401,402] Ciprofloxacin (20 mg/kg/day) compared to placebo reduced febrile episodes in neutropenic pediatric patients during the acute induction phase but not the consolidation phase of chemotherapy for acute lymphoblastic leukemia and was associated with increased stool colonization with ciprofloxacin-resistant *E. coli* and *K. pneumoniae.*[403] Ciprofloxacin and ofloxacin appear superior to norfloxacin,[404,405] with lower rates of gram-negative and, in the case of ofloxacin, streptococcal bacteremias. Addition of penicillin to norfloxacin reduced breakthrough streptococcal bacteremias,[406] and addition of rifampin to ofloxacin reduced staphylococcal bacteremias.[405] Colonization and breakthrough bacteremias with quinolone-resistant viridans streptococci have also been reported when levofloxacin was used alone as prophylaxis in recipients of autologous stem cell transplants and hematologic malignancies.[407,408] Use of additional agents with activity against gram-positive pathogens in combination with fluoroquinolones in prophylaxis can reduce gram-positive bacteremias but is less well tolerated.[409,410] In

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addition, breakthrough bacteremias with quinolone-resistant *E. coli* have occurred as well with fluoroquinolone prophylaxis.[411–413] IDSA guidelines recommend prophylaxis with ciprofloxacin or levofloxacin (the latter preferred in patients with increased risk of mucositis-related streptococcal bacteremia) in high-risk patients, defined as having an expected absolute neutrophil count less than or equal to 100 cells/mm^3 for greater than or equal to 7 days.[400] Relative to historical controls, levofloxacin (10 mg/kg twice daily) reduced febrile episodes in pediatric patients with neutropenia and autologous hematopoietic stem cell transplantation.[414] Reductions in numbers of patients with blood cultures yielding gram-negative bacteria was offset by increases in numbers with blood cultures yielding gram-positive bacteria. Patients who have received quinolone prophylaxis should not be treated with quinolones for fever and neutropenia because of the risk of quinolone resistance.

There is limited experience in using quinolones for treatment of endocarditis.[415] One study reported good responses in intravenous drug abusers with right-sided *S. aureus* (methicillin-susceptible) endocarditis and who complied with the full course of ciprofloxacin (300 mg IV twice daily for 1 week, then 750 mg PO twice daily for 3 weeks), plus rifampin (300 mg PO twice daily for 4 weeks).[416] An additional study compared 28 days of inpatient therapy with ciprofloxacin (750 mg PO twice daily) plus rifampin (300 mg PO twice daily) versus intravenous oxacillin or vancomycin plus gentamicin (given for the first 5 days) for similar patients, with similar response rates for the two regimens when patients were evaluated at 6 to 7 days after completion of therapy.[417] Drug resistance, however, has occurred in this setting, and there have been failures in patients with left-sided *S. aureus* endocarditis. Because of limited case report data, it is not clear if quinolones, such as levofloxacin and moxifloxacin, which would be preferred based on greater activity against susceptible strains of *S. aureus,* would have better outcomes of treatment. There have been a number of single-case reports of patients with gram-negative bacillary endocarditis whose infections have been suppressed with oral quinolones, but there have been failures. Q fever endocarditis, which responds poorly to conventional antimicrobial therapy, has been successfully cured with prolonged courses of ciprofloxacin (12 weeks)[418] or ofloxacin plus doxycycline (4 years).[419] Doxycycline combined with hydroxychloroquine was, however, superior to ofloxacin plus doxycycline.[419] Use of quinolones for endocarditis should currently be limited to circumstances in which established therapies are not possible.

Quinolones vary in their penetration across the blood-brain barrier into CSF.[420] In the presence of meningeal inflammation, concentrations in CSF have reached as high as 39%, 40%, and 60% of peak serum concentrations for ciprofloxacin, levofloxacin, and pefloxacin, respectively.[421,422] In two small studies of patients with predominantly gram-negative bacillary meningitis, pefloxacin (800 mg IV every 12 hours) cured 12 of 16 neurosurgical patients, many of whom had failed to respond to β-lactam therapies,[423] and ciprofloxacin (200 mg IV every 12 hours) cured 18 of 20 similar patients.[424] Ten of 12 neonates with gram-negative bacillary meningitis (and in some cases mixed infections) were also reported to have been cured with intravenous ciprofloxacin (10 to 60 mg/kg/day).[425] Treatment of *P. aeruginosa* meningitis with ciprofloxacin may require very high doses in some patients (800 mg every 8 hours).[426] Use of these quinolones for treatment of meningitis should only be considered in those circumstances in which standard therapies are not possible or have failed. Ciprofloxacin has been used successfully in the treatment of brain abscess caused by *S. enterica* serovar Enteritidis in a small number of case reports.[420] For eradication of nasopharyngeal carriage of *Neisseria meningitidis,* which is indicated in the setting of close contact with patients with meningococcal meningitis, ciprofloxacin (750 mg) or ofloxacin (400 mg) given as a single dose has been highly effective,[427,428] and ciprofloxacin had efficacy similar to rifampin (600 mg twice daily for 2 days) and ceftriaxone (2 g IM).[429] The recent emergence of quinolone-resistant strains of *N. meningitidis,* however, could compromise the efficacy of quinolones for this indication.[430]

Quinolones have been used for treatment of a variety of other infections in small numbers of patients. A few patients with tularemia have responded to ciprofloxacin or levofloxacin,[431,432] and several patients with cat-scratch disease improved more rapidly after ciprofloxacin treatment than might be expected without treatment.[433] Patients with Mediterranean spotted fever caused by *Rickettsia conorii* and Q fever caused by *Coxiella burnetii* may respond to ciprofloxacin or ofloxacin, but doxycycline remains the preferred therapy.[419,434,435] Attempts to treat patients with brucellosis with quinolones have been complicated by a high frequency of relapses,[344,436] but a combination of ofloxacin (400 mg once daily) and rifampin (600 mg once daily) for 6 weeks resulted in a low relapse rate and was comparable to doxycycline plus rifampin.[437] Patients with falciparum malaria have had inconsistent responses to quinolones.[438,439] Ciprofloxacin decreased the BK polyomavirus load in patients who underwent allogeneic hematopoietic stem cell transplantation.[439,440] A double-blind, placebo-controlled randomized study of levofloxacin 500 mg daily as prophylaxis for BK polyomavirus following renal transplant in 154 patients did not find a statistically significant difference in the percentage of patients with viremia at a median of 46 weeks; however, no patient in either group developed BK polyomavirus nephropathy.[441] Ciprofloxacin and metronidazole alone or together have been used in the treatment of inflammatory bowel disease, particularly Crohn's disease, but studies using ciprofloxacin have not shown consistent benefit.[442]

PROBLEMS WITH QUINOLONE RESISTANCE DURING CLINICAL USE

Resistance to fluoroquinolones has been found in many locales throughout the world, but the extent varies in different areas and varies with the pathogen and site of infection.[443] In addition to data from clinical trials, clinical decisions on choice of fluoroquinolones in initial empirical therapy would be best informed initially by local susceptibility data and later by specific susceptibility data on the patient's strain. Development of bacterial resistance among pathogens during clinical use of quinolones is multifactorial. Because spontaneous chromosomal resistance mutations causing resistance increments of fourfold to eightfold for fluoroquinolones may occur at frequencies of 10^{-8} to 10^{-10}, resistance is predicted to occur more often in settings in which there are large numbers of bacteria at the site of infection and the concentration of the drug is below the MIC of the least drug-susceptible mutant subpopulation (a value called the mutant prevention concentration).[31,444,445] Therefore, resistance is more likely in infections caused by less susceptible pathogens, such as *P. aeruginosa* and *S. aureus,* at sites of infection where the bacterial burden is high or at which drug delivery or host eradication mechanisms may be compromised, and in patients who receive inadequate drug doses. Once selected, the rate of amplification of the drug-resistant mutant population will be governed by the degree of resistance conferred by the mutation to the drug being used, the fitness cost that bearing the mutation exacts, the dose of the drug being used, and the duration of treatment.[446]

Epidemiologic factors also affect the extent to which resistant pathogens can spread and thereby amplify the prevalence of resistance.[447] General surveys of resistance patterns occurring over time have found resistance to increase after the introduction of fluoroquinolones and to occur most often with *Pseudomonas* spp. and staphylococci and in soft tissue infections and infections associated with foreign bodies.[448–450] In many medical centers, ciprofloxacin resistance has increased markedly (to <90%) among MRSA but not MSSA strains.[366,451,452] Resistance appears to have been selected in patients colonized with MRSA and given ciprofloxacin for other infections.[366] Clonal dissemination may also contribute to spread of resistance during outbreaks. The community-acquired MRSA strains that have spread into health care systems are more likely ciprofloxacin susceptible, but resistance has occurred in some isolates.[453,454] Susceptibility rates have also decreased among coagulase-negative staphylococci.[455] A similar difference between methicillin-resistant and -susceptible strains has been seen for ciprofloxacin resistance in coagulase-negative staphylococci, and in this setting, cross-selection by exposure to other antibiotics, in addition to direct quinolone selection, appears to augment ciprofloxacin resistance in methicillin-resistant strains, which are usually also multidrug resistant.[456,457]

More surprising has been the emergence of substantial quinolone resistance in initially highly susceptible species of bacteria, particularly *N. gonorrhoeae, C. jejuni,* and *E. coli.* Fluoroquinolone resistance in *N.*

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gonorrhoeae was first identified in the 1990s in some countries in the Far East.[458] The first fluoroquinolone-resistant *N. gonorrhoeae* isolate was found in the United States in 1991. Data from a national sentinel surveillance system showed that fluoroquinolone resistance increased from 0.4% in 1999 to 4.1% in 2003 and to 13.8% in 2006 (www.cdc.gov/std/gisp2006/GISPSurvSupp2006Short.pdf).[459] Reduced susceptibility of *N. gonorrhoeae* to ciprofloxacin was associated with increased likelihood of failure with ciprofloxacin treatment.[460–462] Subsequently, in 2007, the CDC changed its guidance and recommended that fluoroquinolones no longer be used as empirical treatment of gonococcal infections.[173] Quinolone resistance has now also been reported in *N. meningitidis.*[430]

Resistance emerged in *C. jejuni* in human and poultry populations in parallel after quinolone use in both groups in Europe.[463] In the United States, travel to Spain or Latin America was a risk factor for acquiring resistant *C. jejuni,* and the occurrence of domestically acquired cases in patients without prior treatment with a fluoroquinolone also increased. Strain typing has shown an overlap in resistant *C. jejuni* strains from humans and poultry, and contamination of food products with resistant *C. jejuni* has been demonstrated,[464] suggesting contaminated poultry products as the source of some resistant infections in humans. Resistance acquired by an initially susceptible isolate of *C. jejuni* during treatment of *Campylobacter* gastroenteritis with a quinolone has also been reported.[214]

Quinolone-resistant strains of Enterobacteriaceae have emerged among inpatients and outpatients in the United States[465] and globally, in association with fluoroquinolone use.[466,467] Hospital-wide fluoroquinolone use correlated with resistance among *E. coli, K. pneumoniae,* and *Proteus mirabilis.*[465,468] Risk factors in Spanish patients with resistant *E. coli* urinary isolates have included use of quinolones, complicated infections, and use of urinary catheters.[469] Clinically important resistance in *E. coli* has also developed in some hematology-oncology units in Europe in which quinolones were used as prophylaxis during periods of neutropenia[470–472] as well as in nonneutropenic patients in Spain.[473] In these units, breakthrough bacteremias with quinolone-resistant *E. coli* have become problems. These bacteremias as well as colonization of the fecal flora with quinolone-resistant *E. coli*[474] have been associated with quinolone use as prophylaxis and were caused by distinct strains, rather than representing clonal spread within the units. In addition, some patients not receiving quinolones were found to be colonized with quinolone-resistant *E. coli,*[474] and a survey suggested that 25% of the population in Spain may have fecal colonization with such strains.[475] These findings, in conjunction with earlier findings of high rates of colonization of poultry with resistant *E. coli* in Spain,[476] raise the possibility that contamination of the food supply with resistant *E. coli* could be a contributing factor in these areas.[477] Surprisingly, in the United States, fluoroquinolone resistance in extraintestinal *E. coli* isolates has been linked to a clonal lineage with distinctive mutant alleles of *gyrA* and *parC.*[478] Quinolone resistance in *E. coli* bloodstream isolates has been linked with a higher likelihood of initial inappropriate therapy[479] and, in some studies, higher mortality.[480]

With increasing use of quinolones for treatment of patients with respiratory tract infections, there have been concerns about the emergence of quinolone resistance in *S. pneumoniae.* In Canada, ciprofloxacin resistance in isolates of *S. pneumoniae* was 0%, 0.6%, 1.7%, and 4.2% in 1993, 1997–1998, 2000–2001, and 2005, respectively,[481] with the increase between 1993 and 1997–1998 preceded by increasing use of quinolones, largely ciprofloxacin. Resistance to levofloxacin and moxifloxacin also increased significantly, from 0.2% and 0% between 1997 and 1998 to 1.1% and 1.0% in 2005, respectively.[482] Rates of resistance to ciprofloxacin of 15.2% in Northern Ireland and 5.3% in Spain[457] have also been reported. In 2000 in Hong Kong, rates of resistance to ciprofloxacin, levofloxacin, and moxifloxacin were as high as 17.8%, 13.3%, and 8.9%, respectively.[483] Resistant isolates were generally reported in adults but not children, who would be less likely to have received a quinolone, and in noninvasive diseases.[482–484] Although resistant isolates in Hong Kong were clonal, indicating spread from person to person, in Canada, increased genetic homogeneity of resistant clones, as well as de novo mutations, were associated with quinolone resistance,[481–485] and in Spain, the strains were polyclonal. Worrisome was the observation that among the Spanish isolates, 30% of the strains belonged to one of two international, epidemic, multidrug-resistant clones (France9V-3 and Spain23F-1), raising concerns of possible future spread. In the United States, between 1999–2000 and 2001–2002, in one survey, there was a twofold increase in the rate of ciprofloxacin (1.2%–2.7%) and levofloxacin (0.6%–1.3%) resistance, with a significant minority related to widespread quinolone-resistant pneumococcal clones.[486] In different surveys, which also included invasive and noninvasive strains from across the United States, resistance to respiratory quinolones has remained consistently low (0.5%–1.1%) since 1996 and through 2004.[484,487–490]

Several factors potentially account for the variable trends in quinolone susceptibilities. Preferential use of quinolones that have better pharmacokinetic and pharmacodynamic profiles against pneumococci relative to ciprofloxacin could slow selection of resistant mutants.[491,492] In addition, introduction of the pneumococcal conjugate vaccine, which targets drug-resistant pneumococcal serotypes, may have limited the spread of resistant clones. Strains that contain single *parC* resistance mutations are circulating,[493] and these strains, which may be the progenitors of fully resistant strains with dual mutations in *parC* and *gyrA,* would be classified as susceptible and thus are difficult to detect with routine testing.[494] In this background, there is no reason to assume that resistance to newer quinolones will not ultimately emerge among *S. pneumoniae.*[484] Because children are a major reservoir of pneumococci, concerns have been raised that possible future increased use of quinolones in children could increase the rate of development of resistance to quinolones in *S. pneumoniae.*[495]

Resistance to quinolones should be monitored, and strategies for minimizing its occurrence, including focused quinolone use, should be used to avoid compromising the future utility of the class. Prevention of emergence of resistance needs to be addressed in several ways, including monitoring of preexisting chromosomal and transferable mechanisms of resistance; better defining the optimal selected quinolone, dosage, and duration of treatment for particular infections; and infection control to prevent spread of resistant organisms.[445,446,496,497]

ADVERSE EFFECTS

The tolerability of the fluoroquinolones is best assessed in double-blind, randomized trials in which the effects of patient populations, methods of ascertainment, and possible bias can be controlled. In some cases, however, such trials may not have the power to detect adverse effects occurring at low frequency or in more diverse patient populations. In an analysis of 56 such trials, in which fluoroquinolones were compared with placebo or other antimicrobial agents, most studies found similar adverse effect profiles.[498] In a minority of studies, there were either significantly fewer or more adverse effects relative to a variety of comparator agents. In a number of instances, increasing doses and durations of therapy were associated with higher rates of adverse effects. The overall adverse effect profile has been recently reviewed.[499]

The most frequent category of adverse effect involves the gastrointestinal tract, occurring in 3% to 17% of patients in clinical trials. In most patients, anorexia, nausea, vomiting, and abdominal discomfort are mild when they occur. Diarrhea is less frequent, and antibiotic-associated colitis has been rare, possibly because most current quinolones have limited effect on the anaerobic bowel flora.[498,500] Fluoroquinolone use has, however, been a strong epidemiologic risk factor for *Clostridioides difficile* (formerly *Clostridium difficile*)–associated diarrhea in some studies and was particularly noted in outbreaks of the NAP1 strain, which is resistant to fluoroquinolones.[501]

The next most frequent category of adverse effects involves the nervous system, occurring in 0.9% to 11% of patients.[502] Symptoms of mild headache and dizziness have predominated, followed by insomnia and alterations in mood. Hallucinations, delirium, psychosis, and seizures are rare.[503] Seizures may have resulted in some cases from theophylline accumulation or from the ability of theophylline and NSAIDs to augment the ability of quinolones to displace GABA from its receptors.[504] Postmarketing surveillance has also identified uncommon cases of exacerbations of myasthenia gravis occurring after 0.5 to 10 days (median, 1 day) of exposure to various quinolones. The effect is usually reversible within 24 hours of stopping therapy and has recurred with rechallenge.[505] An increased risk (relative risk, 1.83) of peripheral neuropathy was seen in a case-control study of men ages 45 to 80 years. The onset can be

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rapid and resolution variable. The US Food and Drug Administration reissued in 2016 a class warning regarding fluoroquinolone peripheral neuropathy because of additional reports since the 2004 warning that in some cases neuropathy appeared to be permanent. No patient-specific risk factors have been identified, and the mechanism is not known.[506] Although the incidence was very low (1 in 20,000), another case-control study found an increased risk of pseudotumor cerebri in patients receiving fluoroquinolones within 15 to 30 days (adjusted rate ratio, 5.7).[507]

Allergic and skin reactions have occurred in 0.4% to 2.8% of patients in clinical trials overall. Unspecified rashes have been most frequent. With gemifloxacin, rashes developed in 2.8% of patients in clinical trials, but in young women receiving gemifloxacin for 7 or more days, a self-limited, maculopapular rash without biopsy evidence of vasculitis occurred in 14%.[508] In patients with durations of therapy of 5 or less days, rash occurred with low frequency, similar to that of other fluoroquinolones. The occurrence of a rash with gemifloxacin resulted in a somewhat higher rate of rash in response to subsequently given ciprofloxacin (5.9%) relative to placebo (2.0%).[509] Hypersensitivity cross-reactivity among different fluoroquinolones can vary and is difficult to predict,[510] with, for example, reports of patients with prior reactions to moxifloxacin tolerating ciprofloxacin or levofloxacin but not vice versa. Phototoxicity reactions are uncommon with currently used quinolones but can occur in some patients after exposure to ultraviolet A (320–400 nm) light. Earlier quinolones with a halide at position 8, which are no longer available, had higher rates of phototoxicity.[511,512] Delafloxacin appears to have little or no phototoxicity. Drug fever, urticaria, angioedema, vasculitis, serum sickness–like syndromes, and anaphylactoid reactions have been uncommon. Acute interstitial nephritis, probably allergic in origin, also occurs infrequently and has been associated with eosinophiluria but generally not crystalluria. Infiltrates of lymphocytes and eosinophils have been found in the renal interstitium on renal biopsies.[498]

Arthropathy with cartilage erosions and noninflammatory effusions occurs in the weight-bearing joints of juvenile animals given quinolones.[513] Experience with use of quinolones in children has increased, particularly in children with cystic fibrosis given ciprofloxacin.[514] These children and others receiving nalidixic acid, norfloxacin, and ciprofloxacin have only uncommonly had joint symptoms, which have been reversible.[514,515] Studies to identify subclinical cartilage damage by nuclear magnetic resonance imaging of joints of treated children have also been negative.[516] Because of concerns about cartilage toxicity in children, quinolones have not been recommended for routine pediatric use, but there is an evolving view, based on absence of human arthropathy seen over the past decades of fluoroquinolone use, that in some children, particularly those with cystic fibrosis, the benefit of quinolones outweighs what appears to be a small short-term risk of joint toxicity, and expanded use of quinolones in pediatrics is under consideration.[514,517]

Tendinitis with acute onset of pain, swelling, and inflammatory skin changes has been reported in adults given various quinolones[518,519] and has resulted in a highlighted warning in drug safety labeling in the United States. The Achilles tendon is most often involved, and rupture can occur. Symptom onset can be after completion of quinolone therapy. The risks are highest in patients older than 60 years, patients on corticosteroids, and organ transplant recipients.[519–521] In a large patient database, fluoroquinolone use was associated with Achilles tendinopathy (odds ratio, 4.3) and rupture (odds ratio, 2.0).[522] In addition to age and steroid use, female sex and being nonobese were also risk factors. The mechanism of this toxicity is uncertain, but exposure of cultured tendon cells to ciprofloxacin has been associated with increases in expression of matrix metalloproteinases and cellular apoptosis.[523]

Associations with other potential connective tissue toxicities have been reported but cause-and-effect relationships have not been established. Recent large cohort studies show conflicting results with respect to an association of retinal detachment and fluoroquinolone use. In a study of patients who had visited an ophthalmologist in British Columbia, Canada, current use of fluoroquinolones was associated with a 4.5-fold higher risk of developing a retinal detachment, whereas no risk was observed among recent users and past users, and the absolute risk was low.[524] In a study from Taiwan, patients who received oral fluoroquinolones within the preceding 90 days had a twofold higher risk for rhegmatogenous retinal detachment versus amoxicillin users.[525] A larger nationwide, registry-based cohort study in Denmark, however, failed to find such an association; neither current nor recent or past fluoroquinolone use was associated with a significantly increased risk of retinal detachment.[526] In a propensity-adjusted, case-control study from Taiwan, fluoroquinolone use was associated with aortic aneurysm or dissection with an odds ratio of 2.43 for current use and 1.48 for use within 60 days prior.[527] Risk increased with age over 70 years and increased duration of exposure. A cohort study of Canadian patients over the age of 65 years found an adjusted hazards ratio of 2.24 for aortic aneurysm in patients receiving concurrent fluoroquinolones, with a substantially lower risk for amoxicillin.[528] Potential confounding and possible use triggered by symptoms of the condition itself add uncertainty as to any causal relationship with fluoroquinolone use.

Quinolones, to varying extents, can block the potassium channels and thereby delay repolarization in cardiac tissue, an effect that underlies their ability to prolong the QT interval on the electrocardiogram. Prolongation of the QT interval can predispose to ventricular arrhythmias such as torsades de pointes.[529] Older quinolones, sparfloxacin and grepafloxacin, which had QT interval prolongation greater than that of currently available quinolones, were removed from the market in part because of reports of unexpected cardiac events.[529] QT interval prolongation of a lesser magnitude was also found with moxifloxacin, and some increased risk of arrhythmias have been noted in some[530] but not all[531] population-based studies. Ciprofloxacin and levofloxacin have lesser effects on prolongation of the QT interval than moxifloxacin.[532–534] Delafloxacin appears to produce no QT interval prolongation. Additive effects on QT interval prolongation may occur when quinolones are given together with other agents that prolong the QT interval. Thus quinolones should be avoided or used with caution in patients also receiving class III (block potassium channel, e.g., amiodarone, sotalol) or class IA (block potassium and sodium channels, e.g., quinidine, procainamide) antiarrhythmics, or other agents (e.g., erythromycin) that prolong the QT interval. Risk is also potentially increased in the presence of cardiomyopathy, bradycardia, hypokalemia, and hypomagnesemia.[534,535]

Leukopenia and eosinophilia generally occur in less than 1% of patients, and mild elevations in serum transaminases occur in less than 1% to 3% of patients receiving quinolones; these abnormalities are rarely of sufficient severity to require cessation of therapy. An exception occurred with trovafloxacin, which was associated with elevated transaminases in approximately 10% of patients receiving a 4-week course for prostatitis. After release of trovafloxacin for clinical use, rare cases of idiosyncratic, symptomatic hepatitis (1:17,000 reporting incidence) were identified in postmarketing surveillance, some of which were associated with eosinophilic infiltrates and sufficiently severe to cause hepatic failure requiring liver transplantation.[498,536] These events led to the restrictions of trovafloxacin use and later to its withdrawal. Temafloxacin was found through postmarketing surveillance to be associated with rare cases of hemolytic anemia, thrombocytopenia, and renal failure at a reporting incidence of 1 in 5000; such occurrences led to its removal from the market.[537] These severe toxic effects of trovafloxacin and temafloxacin are of uncertain mechanism and have not been seen with currently available quinolones. In a population-based, case-control study of outpatients over age 65 years without a history of prior liver disease, moxifloxacin (adjusted odds ratio, 2.0) and levofloxacin (adjusted odds ratio, 1.85), but not ciprofloxacin, were associated with an increased risk of hospital admission for acute liver injury within 30 days of receiving a prescription relative to clarithromycin.[538]

Although there have been occasional reports of hypoglycemia associated with the use of ciprofloxacin, levofloxacin, and moxifloxacin, cases of severe hypoglycemia associated with use of gatifloxacin in diabetics on oral hypoglycemic agents and other patients have occurred.[539] In addition, hyperglycemia has been reported in elderly nondiabetics receiving gatifloxacin. Various quinolones have been shown to stimulate release of insulin from rat pancreatic islet cells. Although the frequency of dysglycemia appears to be low overall, the relative risk was greater with gatifloxacin than levofloxacin and ciprofloxacin.[540,541] Although systemic gatifloxacin has been withdrawn from the market, topical ophthalmic formulations are still available and have not been associated with dysglycemia.[542]

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Safety in pregnancy[498] has not been established for any of the quinolones, but studies of babies born to women exposed to norfloxacin or ciprofloxacin during the first trimester identified no increase in major malformations, stillbirths, or premature births.[543–545] In one prospective case-control study comparing 200 women exposed to fluoroquinolones and 200 women exposed to known nonembryotoxic antibiotics, there were no differences in birth defects, spontaneous abortions, prematurity, or fetal distress, but there was a higher rate of therapeutic abortions, suggesting that concerns about teratogenic risks may exceed the actual risks.[544] Because quinolones can be excreted in breast milk, they should be avoided for nursing mothers.

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The complete reference list is available online at Expert Consult.

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Update: Safety Update for Fluoroquinolone use from the FDA and Risk of Aortic Aneurysm or Dissection

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Safety Update for Fluoroquinolone use from the FDA and Risk of Aortic Aneurysm or Dissection

December 5, 2020

In 2018, the US Food and Drug Administration issued a class warning regarding fluoroquinolone use, which was noted to have an increased risk of aortic aneurysm or dissection. The background population risk of aneurysm or dissection is low (9 per 100,000 people per year), however in multiple studies, the rates in fluoroquinolone-treated patients were double that of controls.[1,2,3] As such, the FDA recommends avoiding prescribing fluoroquinolones to patients with aortic aneurysms and in patients at higher risk such as those with peripheral vascular disease, hypertension, Marfan syndrome, Ehlers-Danlos syndrome, as well as elderly patients in cases in which other treatment options are available.[4]

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