32 Polymyxins (Polymyxin B and Colistin)

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SHORT VIEW SUMMARY

- The polymyxins are old antibiotics available as polymyxin B and colistin, the latter of which is formulated as its inactive prodrug, colistimethate sodium. They are mainly used intravenously.
- Because of their toxicity (especially nephrotoxicity, with rates ranging from 30% to 60%), they should be reserved for use only as drugs of last resort when dealing with multidrug-resistant bacterial infections.
- These agents act electrostatically by disrupting cell membranes of gram-negative bacilli, and are bactericidal.
- They are highly active against problematic resistant gram-negative aerobic bacilli, namely *Pseudomonas aeruginosa, Acinetobacter baumannii,* and Enterobacteriaceae, although resistance is increasing, and in some settings can be commonplace.
- Resistance is usually mediated via a reduction in the negative charge of the outer membrane; concerningly, plasmid-mediated resistance genes have recently become disseminated.
- Colistimethate sodium (CMS) must be hydrolyzed to colistin in the bloodstream to be active, and this is a slow and inefficient process leading to unpredictable pharmacokinetics.
- Polymyxin B is given as its active form and thus has more reliable and predictable pharmacokinetics.
- The serum concentrations of polymyxins that are required to achieve antibacterial effect overlap with those associated with nephrotoxicity.
- Colistin and polymyxin B undergo extensive tubular reabsorption in the kidney and are eliminated by nonrenal mechanisms. CMS is renally cleared. This leads to the need to renally dose adjust CMS, but not polymyxin B.
- CMS in the urine will hydrolyze to active colistin, making it the preferred polymyxin for urinary tract infections.
- Because of more predictable pharmacokinetics and perhaps less nephrotoxicity, polymyxin B should be preferred over CMS where both are available, with the exception of urinary tract infections.

The polymyxins are among the oldest antibiotics, discovered in 1947. They were used parenterally from 1962 until anti-*Pseudomonas* aminoglycosides (e.g., gentamicin) came into common use after the middle-to-late 1960s.

The polymyxins fell into disuse by 1980 because of their nephrotoxicity and subsequently were reserved mainly for topical and oral use.[1,2] However, the emergence of multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* carbapenem-resistant Enterobacteriaceae (CRE), and other gram-negative bacilli resistant to all other antimicrobial agents has resulted in an increasing need for their use as injectable agents. The two parenteral polymyxins that have been used are polymyxin B and polymyxin E (colistin, formulated as colistimethate sodium [CMS], which is also named colistin methanesulfonate sodium). There are no solid head-to-head studies comparing the effectiveness of CMS and polymyxin B, but comparative toxicity data have begun to emerge. The only direct efficacy comparison was a small retrospective review, which showed similar rates of cure.[3] Unfortunately, this analysis was limited by small numbers, suboptimal dosing, and concomitant antimicrobial exposures. Recent investigations into the comparative toxicity of the polymyxins have suggested that polymyxin B might be associated with lower rates of nephrotoxicity.[4] In recent years, series of patients treated with CMS have been reported in the literature much more frequently than series of patients treated with polymyxin B. However, due to an emerging and growing understanding of the favorable pharmacokinetic parameters and potential safety advantage of polymyxin B,[4,5,6,7] there has been a recent "shift" to preferential use of polymyxin B in areas where both agents are available (such as the United States).

STRUCTURE, SOURCE, AND AVAILABLE PREPARATIONS

The polymyxins are cyclic cationic polypeptide detergents with molecular weights of 1000 Da or greater. Polymyxin B (Fig. 32.1) is derived from products of strains of *Bacillus polymyxa,* and colistin (polymyxin E; Fig. 32.2) is derived from products of *Bacillus colistinus.* The sulfomethylated formulation of colistin, CMS, is an inactive prodrug that must be hydrolyzed to be active as an antibiotic.[8] Hydrolysis occurs at body temperature and within in vitro testing systems. Polymyxin B is available in a parenteral preparation as the active moiety that can be given intramuscularly and intravenously. Polymyxin B is also available for topical use.

Colistin has been available as colistin sulfate for use topically and orally, and as CMS formulations for intramuscular (IM) and intravenous (IV) use. CMS has also been used for inhalation therapy, and CMS and polymyxin B have been administered intrathecally or intraventricularly. CMS and polymyxin B are both available in the United States, whereas other countries typically only have one agent available; colistin sulfate is only available topically.

In the United Kingdom and Europe, CMS and polymyxin B are dosed based on international units (IU), with the rationale that the various preparations have different weights and this can cause confusion (see "Pharmacokinetics" later).

MECHANISM OF ACTION

The polymyxins are surface-active amphipathic agents containing both lipophilic and lipophobic groups. They penetrate into the outer cell membranes of gram-negative bacteria, interact electrostatically with phospholipids in the membranes, and quickly disrupt the membranes via competitive displacement of divalent cations. They also bind to the lipid A portion of cell wall lipopolysaccharide (LPS) and, in animal studies, they block many of the biologic effects of this endotoxin.[9] Resistance in gram-negative bacteria is usually related to modifications of LPS, such as the addition of ethanolamine or aminoarabinose, which lowers the overall charge of the LPS, effectively inhibiting the initial interaction between the positively charged peptides of the polymyxin and the negatively charged LPS.[2] In addition, complete loss of LPS in *A. baumannii* has been reported as a mechanism of bacterial resistance.[10] In 2016, researchers in China identified the first known plasmid-mediated mechanism of colistin resistance, MCR-1,[11] and this has since been

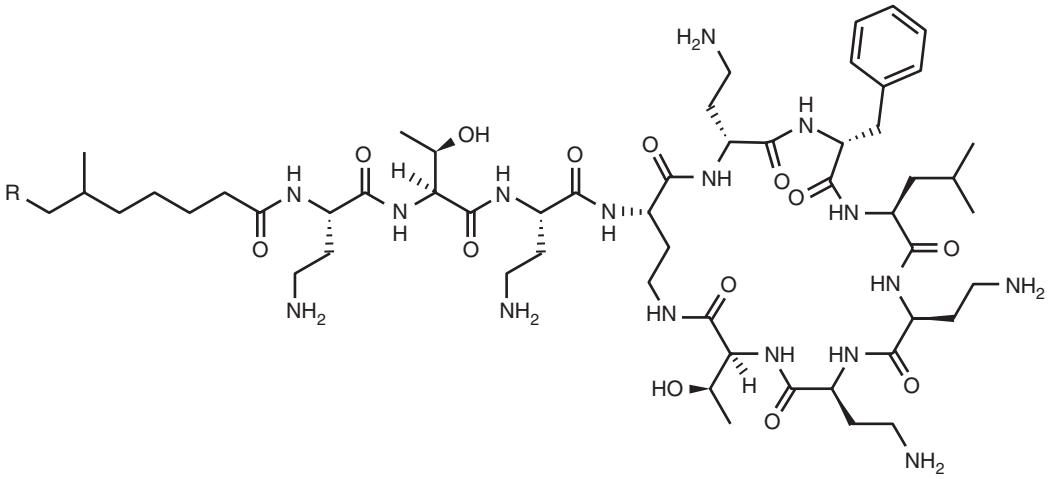

FIG. 32.1 Polymyxin B.

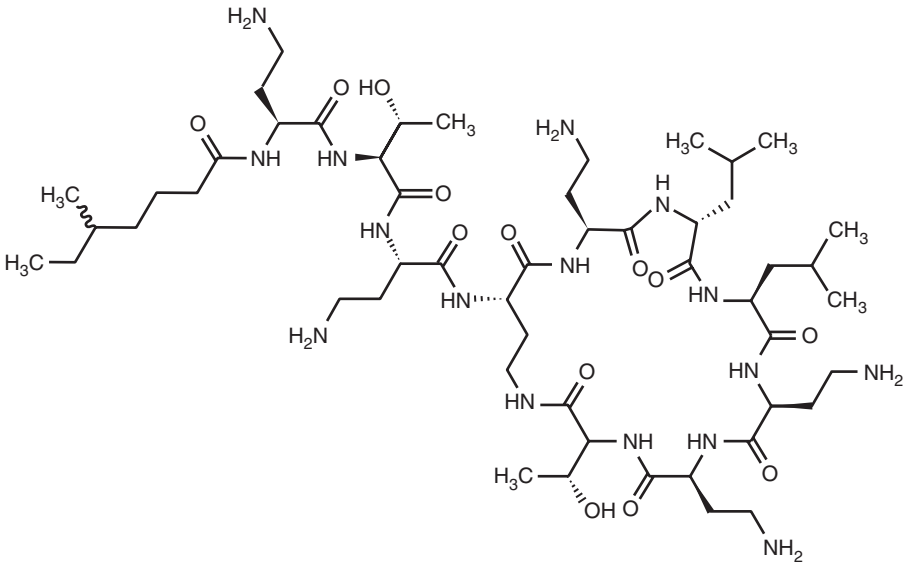

FIG. 32.2 Colistin.

isolated from clinical specimens worldwide. Two other plasmids mediating colistin resistance, MCR-2 and MCR-3, have also been described.

ANTIMICROBIAL ACTIVITY

The polymyxins are active against a broad array of gram-negative aerobic bacilli, with the notable exception of *Proteus* species, most of which are highly resistant. They also have poor activity against *Providencia, Burkholderia, Serratia, Moraxella, Helicobacter, Campylobacter, Vibrio, Brucella, Aeromonas, Morganella,* and *Edwardsiella* species.[2] Gram-positive organisms, gram-negative cocci, and most anaerobes are resistant. The antibacterial activity of the polymyxins is decreased by the presence of divalent cations such as calcium and magnesium. The polymyxins have retained activity against many MDR gram-negative bacilli, such as *P. aeruginosa* and *A. baumannii,* and CRE, with a minimal inhibitory concentration for 90% of isolates (MIC_{90}) often less than or equal to 2 µg/mL. Importantly, however, an increasing number of publications are reporting polymyxin resistance rates exceeding 10%, and, perhaps most alarming, are reports from regions where CRE are epidemic, where more than half of the CRE isolates tested are polymyxin resistant.[12] Furthermore, heteroresistance is common in polymyxin-susceptible strains of these organisms.[13–15] There is complete cross-resistance between different polymyxins.

There is a minor lack of uniformity between susceptibility breakpoints of the Clinical and Laboratory Standards Institute (CLSI) and those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). CLSI has a susceptibility breakpoint for colistin of less than or equal to 2 µg/mL for *P. aeruginosa* and *A. baumannii* but only an epidemiologic cutoff for Enterobacteriaceae (also ≤2 µg/mL). This is in slight contrast to EUCAST, which has clinical breakpoints for colistin susceptibility to each of the aforementioned pathogens of 2 µg/mL. There are no formal breakpoints for polymyxin B, and often clinical laboratories do not have the capability to test polymyxin B susceptibility. This often leads to colistin minimal inhibitory concentrations (MICs) and breakpoints serving as surrogates for polymyxin B. However, data are lacking to support this strategy. Furthermore, there are significant concerns regarding the appropriateness of these breakpoints in light of recently published pharmacokinetic/pharmacodynamic (PK/PD) data (see next two sections).

PHARMACOKINETICS

Neither colistin nor polymyxin B is absorbed when given orally, and oral usage is reserved for selective gut decontamination or decolonization strategies. Distribution of polymyxins to the cerebrospinal fluid, biliary tract, pleural fluid, and joint fluid is poor. The polymyxins are readily dialyzed. Serum levels of the polymyxins are very low after inhalation therapy in cystic fibrosis patients.[16] However, one analysis reported detectable systemic levels in patients receiving CMS at 5 million IU by inhalation every 8 hours.[17]

Pharmacokinetic parameters of intravenous CMS and polymyxin B from the "old" literature are poorly described, and this poor description

TABLE 32.1 Package Insert Dosing Recommendations for Polymyxins

POLYMYXIN PREPARATION	DOSING RECOMMENDATIONS			
	CREATININE CLEARANCE			
	≥ 50 mL/min	30–49 mL/min	10–29 mL/min	<10 mL/min
EMA CMS package insert (based on IU of CMS)	9 MIU (300 mg CBA)/d divided in 2–3 doses	5.5–7.5 MIU (182–248 mg CBA)/d divided in 2 doses	4.5–5.5 MIU (149–182 mg CBA)/d divided in 2 doses	3.5 MIU (116 mg CBA)/d divided in 2 doses
		PLASMA CREATININE		
		0.7–1.2 mg/100 mL	1.3–1.5 mg/100 mL	1.6–2.5 mg/100 mL	2.6–4.0 mg/100 mL
US CMS package insert (based on mg/kg IBW of CBA)[a]	Urea clearance (% of normal)	80–100	40–70	25–40	10–25
	Unit dose of CMS (in mg of CBA)	100–150	75–115	66–150	100–150
	Total daily dose	300 mg divided in 2–4 doses	150–230 mg divided in 2 doses	133–150 mg in 1 or 2 doses	100 mg q36h
	Approximate daily dose,	5 mg/kg/d[b]	2.5–3.8 mg/kg/d	2.5 mg/kg/d	1.5 mg/kg/d
	Normal Dose	**CrCl 20–50 mL/min**	**CrCl 10–20 mL/min**	**CrCl <10 mL/min *or* Hemodialysis**	
Polymyxin B[c] package insert	1.5–2.5 mg/kg/d divided q12h	This amount should be reduced from 15,000 units/kg downward for individuals with kidney impairment.			

[a]Colistin: 1 million IU = 33 mg CBA.
[b]Package insert gives a range of 2.5–5 mg/kg, but the package insert table only lists 5 mg/kg/d.
[c]Polymyxin B: 1 mg = 10,000 IU.
CBA, Colistin base activity; *CMS,* colistimethate sodium; *IBW,* ideal body weight; *IU,* international units; *M,* million.

is one of the major reasons that current package insert dosing regimens are difficult to understand, and, in many cases, inappropriate and inadequate. Modern-day pharmacokinetic data have begun to unravel the mystery surrounding colistin and to a lesser degree polymyxin B pharmacokinetics, and important differences have emerged. Colistin has much more complex pharmacokinetics due to the fact that it is administered in the form of its inactive prodrug methanesulfonate (CMS). It is important to realize that CMS is considered to have no antimicrobial activity until it is hydrolyzed to colistin. The competing elimination of CMS via both hydrolysis to active colistin and renal clearance, which are described in detail next, leads to an extremely complicated and inefficient pharmacokinetic profile for colistin. As is shown next, polymyxin B offers the advantage of much simpler pharmacokinetics due to administration as its active moiety.

Colistimethate Sodium

CMS package insert dosing recommendations differ significantly with regard to which preparation is selected and, with the exception of the recently modified European Medicines Agency (EMA) package insert, are based on levels obtained by nonspecific microbiologic assays of biologic fluids. These assays were unable to differentiate the inactive prodrug, CMS, from the active moiety, colistin. Recent evidence has shown that only approximately 20% of the sum of CMS and colistin in serum is active colistin.[18]

When comparing recommended doses of CMS from different manufacturers, it is important to know that 1 million international units (MIU) equals 80 mg of CMS. It is also essential to understand that although the US product comes in vials containing approximately 360 mg of CMS, the vials are labeled as containing 150 mg "colistin base activity" (CBA), which is equal to approximately 4.5 MIU. In the literature, because of the US labeling, 1 MIU has been considered as equal to approximately 33 mg of CBA. However, the term *colistin base activity* has been challenged as inaccurate because there is no directly available "colistin base" in the vials, but the term is used in this chapter because so much of the literature uses it.[19] The recommended US package insert dosage of CMS for patients with normal renal function is 2.5 to 5 mg/kg of ideal body weight of CBA each day, not to exceed 300 mg CBA daily. Although the package insert limits the daily dose to 300 mg CBA, this limit is often ignored in patients greater than 60 kg in whom doses greater than 300 mg CBA are required to give 5 mg/kg of CBA. In terms of IU, this recommended dosage equates to about 4.5 to 9 MIU/day in a 60-kg person and about 5.3 to 10.6 MIU/day in a 70-kg person, if the 300-mg (9-MIU) limit is ignored. The EMA has updated its package insert based on recent pharmacokinetic evidence. In addition to recommending a 9-MIU (300-mg CBA) loading dose in critically ill patients (rationale described later), they recommend a daily maintenance dose of 9 MIU (300 mg CBA) divided two to three times a day in patients with normal renal function, with a suggestion that doses up to 12 MIU (about 400 mg CBA) might be needed in patients with "good renal function."[20] There are virtually no data available pertaining to dose adjustments in obese patients, and optimal dosing to use in this patient population remains undefined.

Recommendations in the package insert for the dose adjustment of the US CMS product in renal insufficiency are based on plasma creatinine, whereas recommendations for the European product are based on creatinine clearance (Table 32.1).

The controversy and confusion with regard to dosing with renal insufficiency has taken on a new dynamic over the past decade because pharmacokinetic analyses have demonstrated that polymyxin elimination is complex. Although colistin, CMS, and polymyxin B all are filtered by the glomeruli, both colistin and polymyxin B undergo extensive tubular reabsorption, have limited renal elimination in the urine, and are largely eliminated by poorly described nonrenal mechanisms.[5,14,21] On the contrary, CMS does not undergo tubular reabsorption and is primarily eliminated in urine.[14]

Two pharmacokinetic analyses with IV CMS in critically ill patients have enhanced understanding of the pharmacokinetics of CMS.[18,22] Plachouras and colleagues[22] demonstrated that with a CMS dose of 3 MIU (~100 mg CBA) every 8 hours, the predicted peak serum concentration (C_{max}) of active colistin occurred approximately 7 hours after each dose and was only 0.6 μg/mL with the initial dose; the half-life of colistin was 14.4 hours, and at steady state (i.e., after 4–5 half-lives), the C_{max} was 2.3 μg/mL. Therefore a loading dose of 9 to 12 MIU (300–400 mg CBA) was recommended to ensure more rapid attainment of therapeutic concentrations. This finding was in marked contrast to all previous package insert dosing recommendations. The second, much larger analysis by Garonzik and colleagues[18] included patients with renal insufficiency. In their analysis, patients received a wide range of daily doses (median CBA dose, 200 mg/day; range, 75–415 mg/day). The average steady-state concentration of colistin was similar in this analysis (median, 2.36 μg/mL), but there was a wide range of the average steady-state colistin concentrations (0.48–9.38 μg/mL). The higher concentrations were

primarily seen in patients with lower creatinine clearance. However, at all levels of creatinine clearance, there was wide interpatient variability of the serum colistin concentrations obtained, varying up to 10-fold in some instances. The authors demonstrated that the half-life in plasma of CMS increased from a median of 4.6 hours in patients with creatinine clearances >70 mL/min to a median of 11 hours in patients with renal insufficiency, whereas the colistin half-life ranged from a median of 9 hours in those with creatinine clearances >70 mL/min to a median of 13 hours in those with creatinine clearances <10 mL/min. The increase in CMS half-life was not surprising because CMS is eliminated via the kidneys. It was unexpected that the colistin half-life also increased in renal insufficiency because the drug is not eliminated in the urine due to extensive tubular reabsorption. The proposed mechanism for the increase in colistin half-life relates to decreased CMS removal secondary to renal insufficiency. Increased CMS concentrations lead to increased hydrolysis and conversion to active colistin. In total, these findings support the need for dose adjustments based on renal function. The authors also confirmed the need for a loading dose and suggested 5 mg/kg of CBA, with a maximum dose of 300 mg CBA.

It is important to note that while renal dose adjustments are warranted for CMS due to the reasons just outlined, the package insert recommendations for how to accomplish this differ substantially between countries. Compared to the EMA package insert, the US package insert significantly underperforms with regard to its ability to achieve target concentrations due to overreductions in dose when creatinine clearances are <30 mL/min. This underdosing effect is shown in a recent publication in which the authors demonstrate that using the US package insert dosing recommendations in patients with creatinine clearances <30 mL/min would attain the target steady-state concentrations of 2 µg/mL or greater only 10% to 30% of the time.[6]

In early 2017 these same investigators developed a dosing algorithm based on the final results of a National Institutes of Health–funded study.[7] These recommendations are largely in line with the EMA package insert doses and were derived to provide an 80% likelihood of achieving a colistin average steady-state concentration of 2 µg/mL. This target concentration is based on pharmacodynamic data from the mouse thigh model (see "Pharmacodynamics" later) and current susceptibility breakpoints, as well as toxicodynamic data associating average steady-state concentrations of higher than 2 µg/mL with an increased incidence and severity of nephrotoxicity.[23,24] While the target concentration of 2 µg/mL was determined by considering both safety and efficacy, it remains unclear whether this target is optimal (and whether EUCAST and CLSI breakpoints are optimal). It is also important for clinicians to be aware that when patients are described as having "good renal function," often considered to be creatinine clearances ≥80 mL/min, *all* dosing algorithms underperform with regard to attaining the target concentration.[6] This is likely due to enhanced clearance of the prodrug CMS prior to conversion to the active moiety colistin, resulting in subsequent subtherapeutic concentrations of colistin.

Polymyxin B

One milligram of polymyxin B equals 10,000 IU. Although dosing for polymyxin B is simpler and is the same in the United States and elsewhere, no pharmacokinetic rationale for the dosing recommendation is provided in the current package insert, and the dosing recommendation appears to be empirical in nature. The recommended IM dose is 2.5 to 3 mg/kg/day (25,000–30,000 IU/kg/day) in divided doses every 4 to 6 hours, but because IM polymyxin injections cause severe pain, the drug should not be used IM. The recommended IV dose is 1.5 to 2.5 mg/kg/day (15,000–25,000 IU/kg/day) by continuous IV infusion or in divided doses every 12 hours, infused over a period of 60 to 90 minutes.[25] Importantly, however, given the upper range of 3 mg/kg for IM dosing, some experts recommend 3 mg/kg as the upper limit of IV polymyxin B doses. While our knowledge remains limited, recent data have helped to clarify the pharmacokinetics of polymyxin B.[5,21] An analysis of eight critically ill patients given doses of 0.5 to 1.5 mg/kg in 60-minute IV infusions reported peak serum levels ranging from 2.4 to 13.9 µg/mL at the end of the infusion.[21] In a larger study of 24 critically ill patients, dosing by total body weight was found to be superior to dosing by ideal body weight, and the authors suggested that a loading dose would be required to provide an adequate area under the curve (AUC) exposure on day 1.[5] In that study, the half-life of polymyxin B in plasma was 11.9 hours. Based on modeling from these data, average predicted steady-state concentrations with polymyxin B using 2.5- to 3-mg/kg/day dosing would be 3.0 and 3.6 µg/mL, respectively.[16]

The current polymyxin B package insert has no specific recommendations for dose adjustment, and merely states that the dose "should be reduced from 15,000 units/kg/day downward for individuals with kidney impairment."[25] As mentioned earlier, polymyxin B undergoes extensive tubular reabsorption and is not eliminated in urine. The fact that only a small portion is recovered unchanged in urine suggests that, despite package insert recommendations and current practices, dose adjustments in renal insufficiency are not warranted.[5,21] Clinical data support not requiring renal dose adjustments, because doses <1.3 mg/kg/day were associated with increased mortality from infection; the majority of these lower doses were due to unnecessary adjustments in patients with renal insufficiency.[26]

PHARMACODYNAMICS

In vitro, the polymyxins are rapidly bactericidal in a concentration-dependent manner. There is a postantibiotic effect for *P. aeruginosa* but not for *A. baumannii* or *Klebsiella pneumoniae*.[27,28] There is rapid in vitro regrowth of *A. baumannii* and *K. pneumoniae* because of heteroresistance; regrowth also occurs with *P. aeruginosa* but is delayed.[2,13,27,28] The AUC/MIC ratio appears to be the pharmacodynamic parameter that is best associated with bactericidal activity. Data from a neutropenic mouse thigh model suggest that free AUC/MIC exposures of approximately 7 to 17 are associated with 1 to 2 log kill in both *A. baumannii* and *P. aeruginosa*.[29] These data serve as an important foundation for the recommendation that the target average steady-state concentration should be 2 µg/mL. Once protein binding of approximately 50% is taken into account, the average AUC/MIC ratio needed for bactericidal activity is approximately 24 (free AUC/MIC of 12 is a total AUC/MIC of 24 when 50% protein binding is considered). Given the current susceptibility breakpoint of 2 µg/mL, this would suggest the need for a total daily AUC ($AUC_{(0\text{-}24)}$) of 48 mg•h/L (48/2 = 24), which equates to an average steady-state concentration of 2 µg/mL. It is important to note, however, that data from mouse lung infection models are much less encouraging and suggest the need for much higher AUC targets for treatment of *P. aeruginosa* pneumonia. Perhaps even more concerning, even at the highest tolerable dose, bacteriostasis was not obtained in the mouse lung model for *A. baumannii* pneumonia. In addition, concerns exist for the ability to safely achieve higher concentrations, and whether these dosing recommendations and clinical breakpoints are appropriate remains unsettled. For these reasons, it has been suggested that polymyxins be used in combination with another active or synergistic drug.

TOXICITY

Hypersensitivity is unusual. There is dose-related nephrotoxicity, which is often, but not always, reversible after discontinuing the drug. Rates of nephrotoxicity vary greatly in the literature, in part because different definitions of nephrotoxicity are used and because critically ill patient populations are often studied. Modern analyses report rates of nephrotoxicity, as defined by the RIFLE criteria (*r*isk, *i*njury, *f*ailure, *l*oss, *e*nd-stage renal disease), in the 30% to 60% range for both agents.[30–32] Recent evidence has suggested that colistin might have higher rates of nephrotoxicity than polymyxin B.[4] There is also dose-related reversible neurotoxicity manifested by neuromuscular blockade, which can result in muscle weakness and even apnea. Neuromuscular blockade may occur with drug overdosage and in patients with renal insufficiency or those who are receiving curariform drugs, although this is rare. With respiratory paralysis, support of respiratory function is required until the effects of the polymyxin wear off. Intravenous calcium may help reverse apnea. Aminoglycosides may potentiate the neurotoxic effects.

Paresthesias around the lips, tongue, and extremities, as well as peripheral neuropathy and other neurotoxic side effects, are not uncommon.[1] Recent reports have suggested an association between polymyxin B and skin hyperpigmentation.[33,34] Intrathecal and intraventricular administration have generally been well tolerated.

TABLE 32.2 Authors' Dosing Recommendations for Polymyxins Based on Newer PK/PD Information

POLYMYXIN PREPARATION	LOADING DOSE	DOSING RECOMMENDATIONS			
		CrCl ≥50 mL/min	CrCl 30–49 mL/min	CrCl 10–29 mL/min	CrCl <10 mL/min *or* Hemodialysis
		Start 8 hr After Loading Dose	Start 12 hr After Loading Dose	Start 12 hr After Loading Dose	Start 24 hr After Loading Dose
CMS (in mg/kg IBW of CBA): daily dose can exceed 300 mg CBA[a]	5 mg/kg × 1 dose (maximum 300 mg CBA)	5 mg/kg/d divided q8h	3.5 mg/kg/d divided q12h	2.5 mg/kg/d divided q12h	1.5 mg/kg q24h[b]
		Start 12 hr After Loading Dose			
Polymyxin B[c] (in mg/kg ABW)	2.5 mg/kg × 1 dose	2.5 mg/kg/d divided in two equal daily doses[d]			

[a]Colistin: 1 million international units (MIU) = 33 mg CBA.
[b]Colistin and colistimethate are efficiently removed via hemodialysis; therefore doses should be given after dialysis on dialysis days.
[c]Polymyxin B: 1 mg = 10,000 IU.
[d]At the time of publication, the best evidence suggests that renal dose adjustments are unnecessary. Therefore the authors recommend not reducing the dose in the setting of renal insufficiency.[5,21]
ABW, Actual body weight; *CBA,* colistin base activity; *CrCl,* creatinine clearance; *CMS,* colistimethate sodium; *IBW,* ideal body weight; *PK/PD,* pharmacokinetic/pharmacodynamic.

CLINICAL USE

Package insert recommendations for the use of CMS and polymyxin B are listed in Table 32.1. Our recommendations, based on the newer PK/PD information, are found in Table 32.2. For CMS, we find it reasonable for US practitioners to follow the EMA package insert dosing recommendation because it is driven by recent PK/PD data. However, if a clinician prefers to use weight-based dosing, we suggest the renal dosing recommendations found in the Table 32.2. These were extrapolated from the pharmacokinetic data on which the most recent EMA dosing recommendations were based and should provide similar exposures for patients with advanced as well as moderate renal dysfunction. For CMS, 30-minute infusions are commonly used. Assuming normal renal function, we recommend that after giving the loading dose, there should be an every-8-hour administration schedule of 5 mg/kg/day CBA, as detailed in Table 32.2. The EMA is the only label that has pediatric dose recommendations and suggests 75,000 to 150,000 IU/kg/day (2.5–5 mg/kg CBA/day) for patients ≤40 kg.

For polymyxin B, based on recent pharmacokinetic data,[5] we recommend the upper end of the package insert dosing recommendation (2.5 mg/kg/day divided every 12 hours, infused over 60 minutes). In addition, we recommend a loading dose (2.5 mg/kg × 1) and suggest not making any dose reductions based on renal insufficiency.

For treatment of gram-negative bacillary meningitis, polymyxin B has been given intrathecally in doses of 5 to 10 mg/day for the initial 3 days of therapy and then every other day. CMS has been given via the intrathecal and intraventricular routes. The Infectious Diseases Society of America recommends that a CBA dose of 10 mg/day be used via the intraventricular route to treat gram-negative bacillary meningitis.[35] The EMA package insert recommends 125,000 IU/day (~4 mg CBA/day) for intraventricular use. Oral colistin sulfate and polymyxin B have been used for intestinal decontamination. The oral preparation of colistin is not available in the United States.

Inhalation therapy with aerosolized CMS has been used with varying results to treat colonization or infection of the bronchial system in patients with cystic fibrosis, especially with MDR *P. aeruginosa*, often in conjunction with systemic therapy.[36,37] The recommended dose of aerosolized CMS in the EMA is 1 to 2 MIU (33–66 mg CBA) three times daily for all patients ≥2 years of age and 0.5 to 1 MIU (17–33 mg CBA) twice daily for those less than 2 years of age. Although there are no formal US recommendations, clinicians often empirically use a CBA dose of 75 to 150 mg every 12 hours. Recent data suggest that some systemic absorption can occur with inhaled CMS. Nebulization therapy may cause bronchoconstriction; to minimize the risk of bronchoconstriction, CMS should not be premixed until immediately before therapy.[38]

CMS and polymyxin B have been used parenterally to treat systemic infections caused by MDR gram-negative bacilli, often ventilator-associated pneumonia.[36,37,39,40] In general, rates of response to therapy have been similar in patients receiving a polymyxin, compared with patients receiving piperacillin, imipenem, and ciprofloxacin for the treatment of pneumonia caused by *P. aeruginosa*.[36] However, there are conflicting data suggesting inferior outcomes of both polymyxin agents when compared with other antimicrobial classes.[41–43] Use of suboptimal dosing strategies has likely contributed to the poor performance of the polymyxins in some of these studies. Emerging data with novel β-lactam–β-lactamase inhibitor combinations and new aminoglycosides suggest that dose-optimized CMS is clinically inferior to these newer therapies.[44,45] Superinfection with colistin-resistant strains of *Serratia marcescens* and *Stenotrophomonas maltophilia* has been reported.[46]

Because of high toxicity rates that limit the ability to safely achieve PK/PD targets, a still undefined optimal dosing strategy, and questionable current breakpoints for susceptibility, parenteral CMS and polymyxin B should be reserved for use when no other less toxic or potentially more effective drug is available. For serious infections, whenever possible, another agent, preferably one that demonstrates in vitro activity or synergism with polymyxins, should be added to the polymyxin. Because of the more reliable pharmacokinetics and perhaps less toxicity, polymyxin B should be preferred over CMS where it is available, with the exception of urinary tract infection, for which CMS is preferred.

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The complete reference list is available online at Expert Consult.

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33 Linezolid, Tedizolid, and Other Oxazolidinones

Heather L. Cox and Gerald R. Donowitz

SHORT VIEW SUMMARY

- Linezolid and tedizolid are the first two oxazolidinones approved for clinical use by US Food and Drug Administration (FDA).

Linezolid

- FDA-approved for use in adults and children for the following infections caused by susceptible bacteria:
  - Infection with vancomycin-resistant *Enterococcus faecium*
  - Community-acquired and nosocomial pneumonia
  - Uncomplicated skin and skin structure infections
  - Complicated skin and skin structure infections including diabetic foot infections (without osteomyelitis)
- *Unlabeled use:* alternative/adjunctive therapy of mycobacterial and *Nocardia* infections
- *Usual oral or intravenous adult dose:* 600 mg every 12 hours with no dosage adjustment for renal or hepatic dysfunction
- *Drug interactions:* serotonergic and adrenergic agents due to monoamine oxidase inhibition
- *Serious adverse effects:* hematologic toxicity (most commonly thrombocytopenia), lactic acidosis, peripheral and optic neuropathy
- *Resistance:* uncommon but most often associated with 23S RNA G2576T point mutation or acquisition of *cfr* ribosomal RNA methyltransferase; clinically related to previous or prolonged drug exposure or horizontal spread

Tedizolid

- FDA-approved for acute bacterial skin and skin structure infections in adults caused by susceptible isolates of gram-positive microorganisms including *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* group, and *Enterococcus faecalis*
- *Usual oral or intravenous adult dose:* 200 mg daily
- *Drug interactions:* serotonergic and adrenergic agents due to monoamine oxidase inhibition possible, but less likely than with linezolid
- *Serious adverse effects:* similar to linezolid but less likely
- *Resistance:* mechanisms of resistance are similar to those of linezolid, but resistance occurs less commonly; may demonstrate activity against linezolid-resistant strains of *S. aureus,* coagulase-negative staphylococci, and enterococci with the *cfr* gene

The oxazolidinones are a class of antimicrobial agents prepared completely by organic synthesis. In 1978, a patent was issued to E. I. du Pont de Nemours and Company for a series of 5-(halomethyl)-3-aryl-2-oxazolidinones that had antimicrobial activity against plant pathogens. Further manipulation of the molecule led to the development of linezolid, which displayed activity against human pathogens.[1] A number of oxazolidinones are being investigated. Only linezolid (Zyvox) and tedizolid (Sivextro) are approved by the US Food and Drug Administration (FDA) for clinical use.

CHEMICAL STRUCTURE

The basic molecular structure of the oxazolidinones is shown in Fig. 33.1A.[2] The structure-function relationships of these compounds have been reviewed recently.[3,4,5] Manipulation of the A-ring at the C5 position and manipulation of the N-aryl B ring are necessary elements of oxazolidinone antibacterial activity. Fluorination of the B-ring further increases activity. In linezolid (Fig. 33.1B), the acetamide moiety at the C5 position of the A-ring adds to the overall activity of the drug. Tedizolid (Fig. 33.1C) instead contains a hydroxymethyl group at the same position, which serves to preserve activity against linezolid-resistant organisms carrying the *cfr* gene. The favorable minimal inhibitory concentration (MIC) profile of tedizolid is associated with the pyridine (C-ring) and tetrazole (D-ring) moieties. The unique chemical structure of oxazolidinones renders cross-resistance with β-lactams, vancomycin, quinupristin-dalfopristin, and daptomycin unlikely.

MECHANISM OF ACTION

The oxazolidinones are inhibitors of protein synthesis and are usually bacteriostatic, although in some models, bactericidal activity against some organisms has been observed. The mechanism of action is believed to be unique, involving inhibition of the earliest steps of bacterial protein synthesis.[6] These agents bind to the V-domain of the 23S RNA component of the 50S ribosomal subunit. Interaction of oxazolidinones and the A-site of the peptidyl transferase center blocks peptide elongation.[2,7] Binding is competitively inhibited by chloramphenicol and lincomycin, which suggests either shared or overlapping binding sites.[6]

ANTIMICROBIAL ACTIVITY

General Considerations

In vitro assays have established the MICs of linezolid and tedizolid against a variety of organisms. In general, comparisons have shown tedizolid to be two to eight times more potent.[2,3,4,5,8] It is important to recognize that this may not reflect improved clinical activity. Efficacy of both oxazolidinones seems most directly related to the drug concentration area under the curve (AUC)/MIC ratio. Although tedizolid does in fact have lower MICs for most organisms tested, linezolid has higher AUC values, making the AUC/MIC ratio for these drugs similar.[4] Only direct clinical comparisons will be able to determine if one oxazolidinone is actually more effective than another in a specific clinical situation.

Activity Against Gram-Positive Organisms

Both linezolid and tedizolid demonstrate consistent activity against most clinically important gram-positive organisms, such as *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant strains and vancomycin-intermediate and vancomycin-resistant strains); coagulase-negative staphylococci; *Enterococcus faecalis* and *Enterococcus faecium* (vancomycin-susceptible and vancomycin-resistant strains); and streptococci, including penicillin-resistant *Streptococcus pneumoniae* (Table 33.1).[2,4,8,9,10,11,12,13] Tedizolid has consistently lower MICs for these organisms.

A variety of other gram-positive organisms may be susceptible to linezolid or tedizolid, although fewer isolates have been evaluated. These include *Corynebacterium* spp., *Listeria monocytogenes, Bacillus* spp., *Micrococcus* spp., *Erysipelothrix rhusiopathiae, Leuconostoc* spp., *Rhodococcus equi,* and *Pediococcus* spp.[8,14]

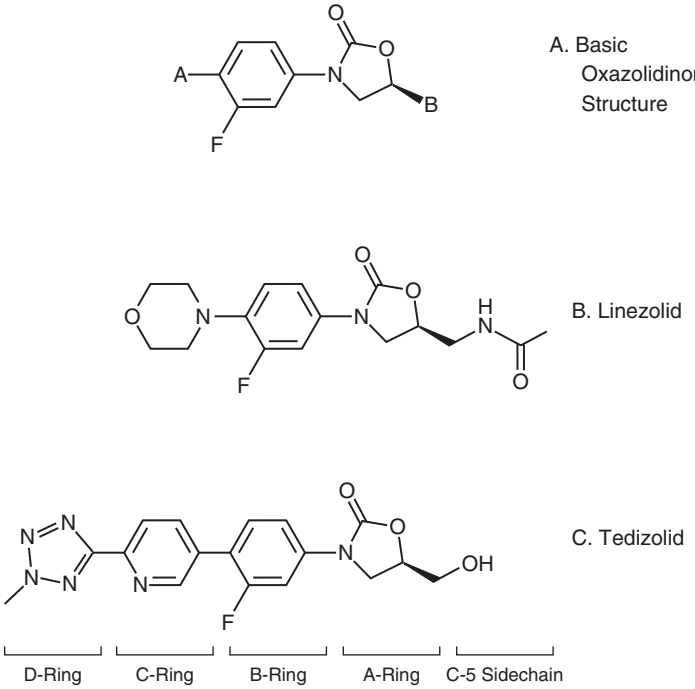

FIG. 33.1 (A) Basic molecular structure of oxazolidinone antibiotics. (B) Structure of linezolid. (C) Structure of tedizolid. *(Modified from Rybak JM, Roberts K. Tedizolid phosphate: a next-generation oxazolidinone.* Infect Dis Ther. *2015;4:1–14.)*

TABLE 33.1 In vitro Susceptibility of Common Aerobic Gram-Positive Organisms to Linezolid and Tedizolid[a]

	LINEZOLID		TEDIZOLID	
ORGANISM	**MIC_{90} (μg/mL)**	**Susceptible (% of Strains)**	**MIC_{90} (μg/mL)**	**Susceptible (% of Strains)**[c]
Staphylococcus aureus				
Oxacillin-susceptible	1–2	100	0.25–0.5	99.9
Oxacillin-resistant	1–2	99.9	0.25–0.5	99.6
Coagulase-negative staphylococci				
Oxacillin-susceptible	0.5–2	99.4	0.25–0.5	—
Oxacillin-resistant	0.5–2	99.1	0.5	—
β-Hemolytic streptococci	1	100	0.25	100
Streptococcus pneumoniae	1	100	0.25	—
Viridans group and other streptococci	1	100	0.25	—
Enterococcus faecalis	2	100	0.5	99.4
Enterococcus faecium				
Vancomycin-susceptible	2	100	0.5	—
Vancomycin-resistant	2	98.5	0.5	—

[a]Data from references 4, 8, 12, and 13.
[b]Clinical and Laboratory Standards Institute susceptibility breakpoints for *S. aureus* are ≤4 μg/mL for linezolid and ≤0.5 μg/mL for tedizolid; for enterococci, ≤2 μg/mL for linezolid and ≤0.5 μg/mL for tedizolid (*E. faecalis* only); for β-hemolytic streptococci, ≤2 μg/mL for linezolid and ≤0.5 μg/mL for tedizolid (*Streptococcus pyogenes* and *Streptococcus agalactiae* only).
[c]Dash indicates no determined breakpoints for susceptibility.
MIC_{90}, Minimal concentration at which 90% of strains are inhibited.

Activity Against Higher Order Bacteria

Linezolid has in vitro activity against a wide number of *Nocardia* spp. with MIC_{90} (minimal inhibitory concentration for 90% of isolates) values of 1 to 4 μg/mL.[15] Virtually all strains tested have proved susceptible. Tedizolid has demonstrated MIC_{90} values several-fold lower than those of linezolid for a number of species with the exception of *Nocardia nova* complex and *Nocardia brasiliensis*, where values were comparable.[16] Limited data suggest that some actinomycete species may be susceptible to linezolid and tedizolid.

Activity Against *Mycobacterium* spp.

The oxazolidinones have demonstrated activity against *Mycobacterium tuberculosis* and a variety of nontuberculous mycobacteria, such as *Mycobacterium avium* complex and *Mycobacterium abscessus* complex, including *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense*.[6,17–20] Tedizolid appears to be more potent for the strains tested, but as with other in vitro analysis, the clinical significance of these findings is unclear.[20] With regard to *M. tuberculosis,* the MIC_{90} of linezolid is on the order of 1 to 2 μg/mL with a review showing lower values of

0.125 to 0.5 µg/mL for susceptible, multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains.[6,17–19,21] Limited data using an intracellular model to assess antituberculous activity have demonstrated that tedizolid is effective against a nonresistant strain.[22]

Activity Against Other Organisms

Most aerobic gram-negative organisms have had no demonstrated susceptibility to oxazolidinones, although not all have been studied. Assessment of potential respiratory tract pathogens has shown that both agents provide incomplete coverage for *Haemophilus influenzae* and *Moraxella catarrhalis*.[3,6,23]

Both oxazolidinones possess activity against gram-positive and gram-negative anaerobic organisms including *Clostridium* spp. and *Bacteroides* spp.[8,10,24] In general, gram-positive anaerobes appear more susceptible, with tedizolid demonstrating the same level of in vitro superiority over linezolid as it does with aerobic organisms. The clinical utility of these agents in infections with these organisms is unclear.

RESISTANCE

Resistance to linezolid was reported before the drug was released in the United States among patients treated for vancomycin-resistant enterococci infections as part of the Linezolid Compassionate Use Program.[25] Despite having been marketed in the United States since 2000, resistance to linezolid remains less than 1%.[12] Resistant strains of staphylococci and enterococci have been reported with prior exposure to the drug and long durations of therapy noted as common predisposing factors.[26,27] Resistance in the absence of linezolid exposure has been described particularly in cases of horizontal transmission or in institutions with high linezolid use.[28–32] Although unusual, outbreaks of infection due to linezolid-resistant bacteria are well described.[27–30] Tedizolid resistance does not appear to be as frequent or as inducible as linezolid resistance. Having been released in 2014, extensive longitudinal data on overall resistance rates of tedizolid are lacking.[4,33] However, over a 5-year period from 2009 to 2013, tedizolid inhibited 99.7% of 11,231 gram-positive isolates from the United States and Europe with MICs ≤0.5 µg/mL.[13]

The most frequent mechanism of resistance involves chromosomal mutations to the oxazolidinone binding site on the 23S ribosomal RNA domain V region. Because bacteria have numerous copies of this gene, multiple mutations are necessary for clinical resistance. Additional binding site modifications resulting from mutations in genes encoding ribosomal proteins L3 and L4 have contributed to resistance in staphylococci, *S. pneumoniae,* and *Clostridium perfringens,* among other pathogens.[34–36]

Non–mutation-related resistance has also been identified among strains of bacteria expressing the acquired *cfr* (chloramphenicol-florfenicol resistance) ribosomal RNA methyltransferase that confers resistance to phenicols, lincosamides, pleuromutilins, and streptogramin A antibacterial agents in addition to the oxazolidinones.[37] The molecular structure of tedizolid allows it to retain antimicrobial activity against some isolates of linezolid-resistant *S. aureus,* coagulase-negative staphylococci, and enterococci carrying the *cfr* gene. However, tedizolid resistance may occur when the *cfr* gene is present in combination with chromosomal mutations associated with linezolid resistance.[4] More recently, a new plasmid-mediated resistance gene, *optrA,* has been identified as a source of linezolid and tedizolid resistance in isolates of *E. faecalis* and *E. faecium*.[38] The gene appears to encode an adenosine triphosphate–binding cassette, giving it a different substrate than the other mechanisms of drug resistance. Initially identified in China, it remains unclear how common this resistance gene is worldwide, which bacterial species may contain it, and how important it is clinically.

PHARMACOLOGY

Linezolid

The approved dose of linezolid for adults and adolescents is 600 mg intravenously or orally every 12 hours for serious infections, with a dose of 400 mg every 12 hours for adults with uncomplicated skin and soft tissue infections. Absorption after ingestion is rapid, with peak serum levels occurring after 1 to 2 hours and bioavailability approaching 100%. The most common dosing regimen of 600 mg intravenously or orally twice daily generates peak serum levels of 15.1 µg/mL and 21.2 µg/mL, respectively.[39] These concentrations represent data from small numbers of healthy volunteers and likely do not represent significant differences between formulations.

Linezolid is 31% bound to plasma proteins. It readily distributes into well-perfused tissues, and penetration into various body sites has been documented in small numbers of patients.[39] Trough cerebrospinal fluid concentrations in patients after neurosurgery and in a patient with meningitis ranged from 1.46 to 7.0 µg/mL with cerebrospinal fluid/plasma ratios greater than 1.[40,41] Peak cerebrospinal fluid concentrations of 3.12 to 12.5 µg/mL have been documented in patients with meningitis.[41,42] Concentrations adequate to treat most relevant pathogens are achievable in pulmonary epithelial lining fluid, alveolar cells, skin, and soft tissue. Bone and joint tissue penetration is more variable.[43]

Linezolid is metabolized by oxidation and appears to interact minimally with cytochrome P-450 enzymes. Urinary excretion accounts for approximately 85% of drug elimination, with 30% as unchanged parent drug. Fecal excretion of its two inactive carboxylic acid metabolites accounts for most of the drug remaining.[39,43] The elimination half-life in adults ranges from 3 to 7 hours.[43] No dose adjustment has been suggested for patients with renal or hepatic insufficiency, but as linezolid and its metabolites are removed by dialysis, administration after hemodialysis is suggested.[39] Similarly, continuous renal replacement therapies also remove linezolid, but no routine change in dosage has been definitively recommended.[44] A prospective, observational study of 30 critically ill patients, some of whom required continuous renal replacement therapies or extracorporeal lung assistance, documented wide variability in serum concentrations that could predispose to clinical failure or toxicity. Dose optimization via therapeutic drug monitoring was proposed.[45] Results from a retrospective analysis of linezolid use in hospitalized patients also recommended therapeutic drug monitoring to optimize therapy, where creatinine clearances of ≤40 mL/min and ≥100 mL/min were associated with overexposure and underexposure, respectively, in multivariate analysis.[46]

Pharmacokinetic and pharmacodynamic parameters most predictive of efficacy are the time above MIC (T > MIC) and AUC/MIC ratio.[43] A study of intermittent versus continuous infusion of linezolid in 18 critically ill patients showed that a continuous infusion was more likely to achieve proposed targets of T > MIC exceeding 85% and AUC/MIC values between 80 and 120. However, the study was not designed to determine clinical efficacy.[43,47]

Linezolid shows some potential for drug-drug interactions. When administered to healthy volunteers in combination with rifampin, a 32% decrease in its AUC was observed.[48] Levothyroxine has resulted in reduced linezolid concentrations as well.[49] Conversely, the addition of clarithromycin produced a more than threefold increase in the linezolid AUC in a patient receiving treatment for XDR *M. tuberculosis*.[50] Some authors have proposed that these effects may be explained by linezolid acting as a P-glycoprotein substrate.[50,51] Linezolid overexposure has also been documented with concomitant administration of amlodipine, amiodarone, and omeprazole, whereas an increase in the international normalized ratio was observed among 6 patients receiving warfarin following cardiac surgery.[52,53] Drug-drug interactions with serotonergic and adrenergic agents are discussed later in "Untoward Reactions."

Tedizolid

Tedizolid phosphate (TR-701) is a prodrug converted in vivo by plasma phosphatases to active tedizolid (TR-700) following oral and intravenous administration. The phosphate group enhances aqueous solubility, whereas an absolute bioavailability of 91% permits no dosage adjustments between formulations. Peak serum levels following 200 mg oral and intravenous doses are 1.8 to 2.4 µg/mL and 2.6 to 3.5 µg/mL, respectively. Its half-life of approximately 12 hours supports once-daily dosing, and the oral product can be taken without regard to meals. Plasma protein binding is 70% to 90%, whereas adipose and skeletal muscle tissue penetration results in exposure similar to free drug in plasma. Relative pulmonary distribution in healthy volunteers was higher with AUC ratios of penetration into epithelial lining fluid and alveolar macrophages versus plasma of 40 and 20, respectively. Tedizolid is primarily metabolized by the liver and eliminated in feces as an inactive sulfate conjugate with only 18% excreted unchanged in urine. Pharmacokinetic parameters

are similar for patients with hepatic impairment, renal insufficiency (including patients on hemodialysis), and in the setting of obesity (body mass index ≥30 kg/m^2).[3,54,55] Thus no dosage adjustment has been deemed necessary for any of these special populations.

The free AUC/MIC ratio most closely predicted tedizolid efficacy in murine models of infection. However, markedly decreased antistaphylococcal activity was observed compared with linezolid in granulocytopenic mice,[56] emphasizing that its safety and efficacy in the setting of neutropenia have not been established. Higher tedizolid exposure for achievement of similar effects in a murine model of pneumococcal lung infection was also required in the absence of granulocytes, although the difference was much less pronounced.[57]

Tedizolid does not appreciably interact with cytochrome P-450 enzymes but is known to inhibit intestinal breast cancer resistance protein (BCRP) and increase serum concentrations of orally administered BCRP substrates. For example, coadministration of tedizolid increased the maximum concentration of the BCRP substrate, rosuvastatin, by 55%, and its AUC by 70%.[54] Drug interaction potential with serotonergic and adrenergic agents is discussed later in the chapter.

CLINICAL USE

Linezolid

Linezolid was approved by the FDA in April 2000 for adults and children with a variety of clinical infections involving susceptible gram-positive organisms. Current FDA-approved indications include (1) nosocomial pneumonia caused by methicillin-resistant (MRSA) or methicillin-susceptible (MSSA) *S. aureus* or *S. pneumoniae;* (2) community-acquired pneumonia caused by *S. pneumoniae* including cases with concurrent bacteremia or MSSA; (3) complicated skin and skin structure infections including diabetic foot infections without concomitant osteomyelitis caused by *S. aureus* (MRSA or MSSA), *Streptococcus pyogenes,* or *Streptococcus agalactiae;* (4) uncomplicated skin and skin structure infections caused by MSSA or *S. pyogenes;* and (5) vancomycin-resistant *E. faecium* infections including those with concurrent bacteremia.[39]

Tedizolid

Tedizolid has been approved for clinical use since 2014 for use in adults with skin and skin structure infections caused by susceptible organisms including MRSA and MSSA, *S. pyogenes, S. agalactiae*, *Streptococcus anginosus* group, and *E. faecalis*.[54] Therapy with linezolid and tedizolid for infections caused by specific organisms is described in the following paragraphs.

Staphylococcus aureus Including Methicillin-Resistant *S. aureus*

Linezolid

Skin and skin structure infections are the most common staphylococcal infections for which the oxazolidinones are used. MRSA has received the most attention because effective antibiotic choices are more limited.

Linezolid has been shown to be as effective or superior to other antibiotics in this patient group. In a Cochrane review of 9 of 33 trials comparing linezolid versus vancomycin for skin and soft tissue infections, linezolid was shown to produce superior clinical and microbiologic cure rates as well as shorter hospital stays and lower overall cost.[58] Subgroup analysis revealed that this superiority was true for both MRSA and MSSA but was observed only in adults and not in patients <18 years of age. Overall, the studies analyzed were thought to be of poor methodologic quality with potential for publication bias, suggesting that further investigation is needed to more clearly establish the superiority of any given regimen over another.[58] Adverse effects may also be more common with linezolid.[14]

Another major area of interest for linezolid use has been for treatment of nosocomial pneumonia involving MRSA. In pooled data from two randomized, double-blind studies, linezolid in combination with aztreonam proved equivalent to vancomycin plus aztreonam for treatment of nosocomial pneumonia in which S. *aureus* (both MSSA and MRSA) and *S. pneumoniae* were the most commonly isolated gram-positive pathogens.[59] Subgroup analysis revealed that linezolid was associated with significantly higher cure rates and improved survival when considering only patients treated for MRSA infection. The subgroup analysis and therefore the results of this study have been questioned.[60]

When the same authors conducted a prospective, double-blind, multicenter study of linezolid versus vancomycin, they again found that linezolid was superior. However, as more patients randomly assigned to vancomycin were mechanically ventilated and had MRSA bacteremia, and the median vancomycin serum trough concentrations on day 3 were suboptimal, questions regarding the validity of the findings were again raised.[61]

In the most recent of several meta-analyses comparing linezolid with vancomycin, one looking specifically at MRSA nosocomial pneumonia and including nine randomized controlled studies, no differences in clinical or microbiological efficacy or all-cause mortality were noted.[62] There were no significant differences in adverse events including gastrointestinal toxicity and thrombocytopenia between the groups studied. The only significant difference in toxicity between groups was the higher incidence of nephrotoxicity in the vancomycin-treated patients, a finding that was noted previously.[61] Although none of the studies has been viewed as definitive, this analysis seems to be the most complete at the present time.

Although levels of evidence vary, guidelines for the treatment of MRSA infection in adults and children recommend linezolid as initial or alternative therapy for complicated skin and soft tissue infections, pneumonia, bone and joint infections, and central nervous system infections and for select patients with persistent bacteremia, vancomycin treatment failure, or both.[63] Several studies have suggested that linezolid may be effective salvage therapy in patients with MRSA bacteremia who fail to respond to vancomycin; however, this use has not been clearly established.[64,65] Linezolid use in endovascular infections with MRSA including endocarditis has yielded inconsistent results, and guidelines have not listed linezolid as suggested therapy for MRSA endocarditis.[66,67]

Tedizolid

Major clinical use of tedizolid thus far has been in skin and soft tissue infection. Two trials have compared tedizolid with linezolid; only oral formulations were used in one trial, whereas in the other, intravenous formulations could have been used before changing to the same oral product.[68,69] Tedizolid 200 mg once daily was used for 6 days and compared with linezolid 600 mg twice daily for 10 days. *S. aureus* was the most commonly isolated organism, with MRSA isolated in 27% to 42% of infections. In both trials, tedizolid was noninferior to linezolid using an initial assessment of response at 48 to 72 hours and subsequent assessments at the end of therapy. Although the overall incidence of drug-related toxicity was similar, gastrointestinal adverse effects (nausea, vomiting, diarrhea) were less common in tedizolid-treated patients. Thrombocytopenia was uncommon in both groups but was less frequent with tedizolid. Pooled data from both studies were analyzed and led to similar findings.[70]

Tedizolid has also been compared with other agents used in skin and skin structure infections. In a network meta-analysis of 15 randomized clinical trials of skin and skin structure infections, the clinical response to tedizolid was superior to that of vancomycin but comparable to other agents including linezolid, tigecycline, ceftaroline, teicoplanin, daptomycin, and telavancin.[71] Drug-related adverse events did not differ between any of the agents reviewed. The heterogeneity of the studies and differences in proportion of MRSA infections in each all lead to a limited interpretation as to the comparable efficacy of tedizolid versus the other agents. A phase III randomized controlled trial of tedizolid versus linezolid for treatment of adults with gram-positive hospital-acquired or ventilator-associated pneumonia is underway.[72]

Coagulase-Negative Staphylococci

Case reports and case series have described cure after linezolid therapy for bone and joint infection, meningitis, ventriculoperitoneal shunt infections, and endocarditis caused by coagulase-negative staphylococci, often in the setting of prosthetic material[73–76]; there are inadequate data to recommend linezolid routinely for initial treatment. Although small numbers of coagulase-negative staphylococcal infections have been treated with tedizolid, no statements can be made regarding its overall clinical utility.

Vancomycin-Resistant Enterococci

Linezolid has been shown to be effective for treatment of infection with vancomycin-resistant enterococci. Successful treatment of bacteremia,[77] endocarditis,[73] peritoneal dialysis–related infections,[78] osteomyelitis,[75] endophthalmitis,[79] ventriculitis,[76] meningitis,[41,42,76,80] intraabdominal infections,[81] and urinary tract infections[81] has been reported, although failures have occurred.[81–83] Clinical data are insufficient to denote superiority among available agents. Linezolid has been compared with daptomycin, the other drug commonly used for these infections. Although several meta-analyses have reported linezolid superiority, limitations of the studies included have hindered the conclusions that could be drawn.[84–86] A retrospective cohort study carried out within the US Department of Veterans Affairs health care system found contradictory results with daptomycin used at even relatively low doses, showing higher clinical success rates and lower 30-day mortality.[87] At the present time, antibiotic selection for these infections should be individualized and based on considerations such as in vitro susceptibility of the organism, antecedent antibiotic exposure, source of infection, comorbidities, and potential for drug-related toxicity. With regard to linezolid use for vancomycin-resistant enterococcal endocarditis, despite its being bacteriostatic, there have been cases of treatment success and failure. Linezolid is recommended for therapy, as is daptomycin, for endocarditis caused by enterococci (usually *E. faecium*) resistant to penicillin, aminoglycosides, and vancomycin. The strength of the recommendation is limited by small numbers of patients and should not be viewed as a well-established guideline.[66]

Tedizolid

The in vitro characteristics and pharmacodynamic properties of tedizolid suggest that it would be useful for vancomycin-resistant enterococci infections including some linezolid-resistant strains. Only case reports and abstracts are described, so its overall efficacy is yet to be determined.[88,89]

Streptococci Including *Streptococcus pneumoniae*

Linezolid

The efficacy of linezolid against *S. pneumoniae* has been demonstrated in open-label trials involving community-acquired pneumonia in hospitalized adults and children and in a controlled multicenter study.[59] Despite approval of linezolid for treatment of pneumococcal community-acquired pneumonia, it has been noted that limited activity against *Haemophilus influenzae* and inconsistent activity against *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* should preclude its use as first-line empirical therapy.[6]

Data describing the efficacy of linezolid for pneumococcal central nervous system infection are limited to case reports and case series and largely involve its use in combination with ceftriaxone for penicillin-nonsusceptible isolates. In a single case, a postsurgical cerebral abscess caused by penicillin-susceptible *S. pneumoniae* was treated successfully with linezolid.[76] Linezolid has also been used successfully for treatment of skin and soft tissue infections caused by streptococci including *S. pyogenes* and *S. agalactiae.*[14]

Tedizolid

Streptococcal infection involving skin and skin structures has been successfully treated with tedizolid in the ESTABLISH-1 and ESTABLISH-2 trials. Although *S. aureus* including MRSA was isolated most commonly, *S. pyogenes, S. anginosus* group organisms, *S. agalactiae,* and *Gemella morbillorum* were isolated and treated successfully.[68,69] Response rates to tedizolid were lower in patients with infections with *S. anginosus* group organisms compared with linezolid (70% vs. 89%), although numbers were insufficient to determine statistical significance.[70] The role of tedizolid for other streptococcal infections including those caused by *S. pneumoniae* has not yet been established.

Mycobacterium Including *Mycobacterium tuberculosis*

Linezolid

Linezolid demonstrates in vitro bacteriostatic activity against *M. tuberculosis,* including MDR and XDR strains. In vitro studies of linezolid with first-line and second-line antituberculous agents usually reveal additive rather than synergistic interactions.[90,91] In small numbers of patients with infection caused by MDR and XDR *M. tuberculosis,* the addition of linezolid to failing regimens led to sterilization of sputum after 4 to 6 months of therapy in 89% of patients, with sputum remaining negative 1 year after therapy in 71%.[92,93] Systematic reviews and meta-analysis of the use of linezolid in patients with MDR and XDR tuberculosis have reported similar success rates. Adverse events with linezolid, especially marrow toxicity and neuropathies, are commonly reported due to the need for extended use, leaving unanswered questions as to the best dosing regimen and means of toxicity monitoring in these patients.[94,95]

Tedizolid

Although in vitro activity of tedizolid is similar to that of linezolid and its safety profile suggests it may be used with fewer adverse reactions, published clinical data in patients infected with *M. tuberculosis* are lacking.

Nocardia spp.

Linezolid

Small case series and case reports have demonstrated the efficacy of linezolid for treatment of *Nocardia* infections including central nervous system disease in immunosuppressed and immunocompetent hosts.[96–99] It has been used both as monotherapy and in combination regimens. Adverse events including cytopenia are commonly reported especially with long-term therapy and the usual dosing regimen. Lower doses have been successfully used with the implication that adverse events may be avoided by less drug exposure.[100]

Tedizolid

There are few data regarding use of tedizolid in patients with *Nocardia* infections. It has been used successfully in central nervous system disease, but its overall utility in these infections and its efficacy compared with linezolid require further testing.[101]

UNTOWARD REACTIONS

Both linezolid and tedizolid are relatively well tolerated, with headache, diarrhea, nausea, and vomiting predominating in larger clinical trials.[39] Serious but less common adverse events are discussed next.

Hematologic Toxicity

Reversible myelosuppression, including pure red blood cell aplasia, pancytopenia, and especially thrombocytopenia, has been clearly documented and related to linezolid use.[102] Thrombocytopenia is most common, and although the mechanism is not definitively established, both a drug-induced immune-mediated phenomenon and inhibition of platelet progenitor cells have been suggested.[103,104] Adults completing phase III clinical trials developed thrombocytopenia in 2.4% of cases (range, 0.3%–10%), but the risk is increased with prolonged durations of therapy and renal insufficiency.[39,43,105] Furthermore, delayed neutrophil recovery and worsening thrombocytopenia have been documented in patients with baseline marrow suppression.[106,107] Anemia appears to be caused by suppression of normal erythropoiesis, similar to the marrow effect of chloramphenicol.[104] Weekly monitoring of hematologic parameters is therefore recommended, particularly for therapeutic durations exceeding 2 weeks.[39] Thrombocytopenia occurred in 6.4% of patients treated with tedizolid compared with 12.6% receiving linezolid in a phase III study.[54] No hematologic toxicity was observed among healthy volunteers given tedizolid for 21 days.[108] Correction of linezolid-associated myelotoxicity following a change to tedizolid has also been described.[109]

Monoamine Oxidase Inhibition

Linezolid is a reversible, nonselective monoamine oxidase inhibitor and has been associated with the development of serotonin syndrome (fever, agitation, mental status changes, tremors) in patients receiving concurrent serotonergic agents.[39,110] Small increases in systolic blood pressure have been documented in patients receiving tyramine concurrently with linezolid, leading to recommendations for dietary restriction. Similarly, blood pressure monitoring is recommended for patients taking

adrenergic agents such as pseudoephedrine and phenylpropanolamine.[39] Tedizolid exhibits weak, reversible monoamine oxidase inhibition as well. Although patients receiving concurrent serotonergic agents were excluded from phase II and III study, neither human nor animal model investigation revealed adverse hypertensive or serotonergic effects at therapeutic dosing.[43]

Adverse Effects Associated With Mitochondrial Toxicity

Disruption of mitochondrial protein synthesis has been viewed as the explanation for linezolid-induced neuropathies and lactic acidosis, both of which are described in more detail subsequently.[110–112] Case reports of suspected linezolid-associated rhabdomyolysis and drug-induced liver injury have also raised the possibility of mitochondrial toxicity as an etiology.[113,114] Although tedizolid is thought to be a more potent mitochondrial protein synthesis inhibitor, it has been proposed that less free drug exposure and a period of mitochondrial recovery during each dosing interval may decrease the risk of associated toxicity.[115] More study is needed to confirm these findings in humans.

Neuropathy

Linezolid-induced neuropathies are well documented.[110] Peripheral neuropathy may begin with dysesthesias in the hands and is poorly reversible. Optic neuropathy causes gradual onset of blurring and can lead to permanent loss of useful visual acuity if the drug is not discontinued; when detected early, visual loss has generally been reversible. Peripheral neuropathy and optic nerve disorders in a phase III study of patients receiving tedizolid for 6 days or linezolid for 10 days occurred with similar frequency.[54] When healthy volunteers received tedizolid for 21 days, no evidence of neuropathy was observed.[117]

Lactic Acidosis

Lactic acidosis, including fatal cases, has been reported most commonly during prolonged durations of linezolid therapy but can develop within the first week.[110,118] Prompt recognition and drug discontinuation are critical. Age, renal insufficiency, and drug interactions associated with linezolid overexposure increase the risk. The possibility of genetic predisposition has also been suggested.[116] No postmarketing cases of tedizolid-associated lactic acidosis have been reported to date.

Miscellaneous Untoward Reactions

In patients treated with linezolid for intravascular catheter-related infections, increased mortality was observed in the setting of gram-negative infection, mixed gram-positive and gram-negative infections, or no clear infection at the time of therapy.[113] The poor gram-negative activity of linezolid should limit its use as a single agent in clinical situations that may involve these organisms. Increased mortality with no clear infection remains to be explained.

Other notable yet rare postmarketing reports of adverse effects with linezolid include posterior reversible leukoencephalopathy syndrome, seizures, tooth and tongue discoloration, black hairy tongue (lingua villosa nigra), and hypoglycemia among diabetic patients receiving insulin or oral hypoglycemic agents.[39,114,119,120]

LINEZOLID VERSUS TEDIZOLID

At the present time, tedizolid is approved by the FDA only for therapy of skin and skin structure infections. As its efficacy appears similar, the convenience of once-daily dosing for a shorter duration of therapy and a reduced average wholesale price (for a 6-day course of tedizolid vs. a 10-day course of linezolid) may precipitate increased clinical use in this setting. Although an economic advantage may dissipate when durations of therapy are equivalent, tedizolid could offer an improved adverse effect profile when prolonged administration is required. However, its role in comparison with linezolid for other infections has not yet been established due to a paucity of clinical experience.

OTHER OXAZOLIDINONES

Cadazolid (formerly ACT-179811) is a nonabsorbable quinolonyl-oxazolidinone active against *Clostridioides difficile* (formerly *Clostridium difficile*), including hypervirulent epidemic strains as well as strains resistant to fluoroquinolones and linezolid. A phase II study of patients with *C. difficile* infection found similar clinical cure rates and tolerability when comparing three dosages with oral vancomycin as an active reference.[121] A phase III multicenter, randomized, double-blind study of a 250-mg oral suspension given twice daily versus oral vancomycin has since been performed.[122] Compounds completing phase II study include radezolid (RX-1741) for mild-to-moderate community-acquired pneumonia and uncomplicated skin and skin structure infections and sutezolid (PNU-100480) for treatment of infection with *M. tuberculosis*.[123–125]

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34 Sulfonamides and Trimethoprim; Trimethoprim-Sulfamethoxazole

Stephen H. Zinner and Kenneth H. Mayer

SHORT VIEW SUMMARY

- Among the earliest antimicrobial compounds in clinical use, sulfonamides still remain useful for the treatment of urinary tract infections and infections caused by *Nocardia* species, atypical mycobacteria, and *Toxoplasma gondii*.
- The most common adverse reactions to sulfonamide include leukopenia, thrombocytopenia, acute hemolytic anemia, nausea, vomiting, rash, and fever.
- Serious but less common adverse reactions include agranulocytosis, aplastic anemia, acute tubular necrosis, interstitial nephritis, drug-induced lupus, toxic epidermal necrolysis, and Stevens-Johnson syndrome. The risk of kernicterus precludes the use of sulfonamides in late pregnancy.
- Today, sulfonamides are most frequently used with trimethoprim as a fixed-dose combination of 160 mg/800 mg of trimethoprim-sulfamethoxazole (TMP-SMX).
- TMP-SMX is useful in the treatment of *Stenotrophomonas maltophilia, Pneumocystis jiroveci, Listeria monocytogenes, Cystoisospora belli,* leprosy (as part of combination therapy), urinary tract infections, prostatitis, acute exacerbations of chronic bronchitis, methicillin-resistant staphylococcal skin and soft tissue infections, and malarial infections caused by susceptible organisms.
- TMP-SMX is indicated for the prophylaxis of *P. jiroveci* in immunocompromised patients, including those with human immunodeficiency virus (HIV) infection.
- The adverse effects of TMP-SMX are similar to those seen with sulfonamides alone and may be more frequent in HIV-infected patients.
- Iclaprim is an investigational diaminopyrimidine with enhanced activity against gram-positive cocci, including trimethoprim-resistant strains.

The modern era of antimicrobial chemotherapy began in 1932 with the first reports by Domagk of the protective activity of sulfachrysoidine (Prontosil) against murine streptococcal infections. This drug was developed initially by the German dye industry and had been available commercially since the early 20th century. Sulfachrysoidine exerted its antibacterial activity through the release in vivo of para-aminobenzenesulfonamide (sulfanilamide). This was the first antibacterial agent used in the United States, in July 1935, in an unsuccessful attempt to treat a 10-year-old girl late in the course of meningitis and sepsis caused by *Haemophilus influenzae*.[1] During the late 1930s, the basic sulfanilamide compound was modified to remove unpleasant side effects and expand its spectrum of activity, resulting in compounds with distinctive properties—for example, compounds that are concentrated in the kidney for the treatment of urinary infections or nonabsorbable compounds for increased activity within the gastrointestinal tract.

Trimethoprim is a 2,4-diaminopyrimidine that inhibits dihydrofolate reductase (DHFR), resulting in interference in folic acid and pyrimidine synthesis in the bacterial cell. Trimethoprim was one of several such compounds synthesized and studied by Hitchings and coworkers in the 1950s and 1960s. The use of trimethoprim as a potentiator of sulfonamide activity was introduced by Bushby and Hitchings[2] in 1968. In the subsequent decade, the combination of trimethoprim-sulfamethoxazole (TMP-SMX) was introduced clinically and gained a role in chemotherapy for many infectious diseases. TMP-SMX, available in a fixed drug combination, shows true antibacterial synergism against a wide variety of organisms.

SULFONAMIDES

Structure

The clinically useful sulfonamides are derived from sulfanilamide, which is similar in structure to para-aminobenzoic acid (PABA), a compound required by bacteria for folic acid synthesis (Fig. 34.1). A free amino group at the 4-carbon position is associated with enhanced activity. Increased activity caused by increased PABA inhibition is associated with substitutions at the sulfonyl radical (SO_2), which is attached to the 1-carbon, as seen with sulfadiazine, sulfisoxazole, and sulfamethoxazole, all of which are more active than the parent compound, sulfanilamide. The nature of these substitutions determines other pharmacologic properties of the drug, such as absorption, solubility, and gastrointestinal tolerance. Substitutions at the 4-amino group result in decreased absorption from the gastrointestinal tract (e.g., phthalylsulfathiazole).

Derivation and Nomenclature

Since the introduction of sulfonamides into clinical medicine, dozens of compounds have been used. Relatively few survive today, however. The various compounds can be classified as (1) short-acting or medium-acting sulfonamides, (2) long-acting sulfonamides, (3) sulfonamides limited to the gastrointestinal tract, or (4) topical sulfonamides. Many branded sulfonamide preparations have been discontinued or replaced by generic products.

Short-Acting or Medium-Acting Sulfonamides

Sulfisoxazole (*United States Pharmacopeia* [USP]), sulphafurazole *(British Pharmacopeia), and* *N*′-(3,4-dimethyl-5-isoxazolyl) sulfanilamide are available to treat urinary infections. Sulfamethoxazole USP, *N*′-(5-methyl-3-isoxazolyl) sulfanilamide, is less soluble than sulfisoxazole and yields higher blood levels. It is the sulfonamide most frequently combined with trimethoprim. Sulfadiazine USP (*N*′-2-pyrimidinylsulfanilamide) is highly active, attains high blood and cerebrospinal fluid levels, and is associated with low protein binding and lower solubility than the previously mentioned drugs.

Short-acting sulfonamides also are available in several combinations. Sulfisoxazole and sulfamethoxazole have been combined with phenazopyridine, a urinary analgesic.

Long-Acting Sulfonamides

Sulfamethoxypyridazine (*N*′-[6-methoxy-3-pyridazinyl] sulfanilamide) and sulfameter (*N*′-[5-methoxy-2-pyrimidinyl] sulfanilamide) are no longer available for single-daily-dose therapy because they were associated with hypersensitivity reactions such as Stevens-Johnson syndrome. Neither sulfadimethoxine nor any other long-acting sulfonamide, other than sulfadoxine, is currently available in the United States.

Sulfadoxine, originally known as *sulformethoxine* (*N*′-[5,6-dimethoxy-4-pyrimidyl] sulfanilamide), is a very-long-acting sulfonamide that, combined with pyrimethamine, was formerly available in the United States. Sulfadoxine has a half-life of 100 to 230 hours and reaches a

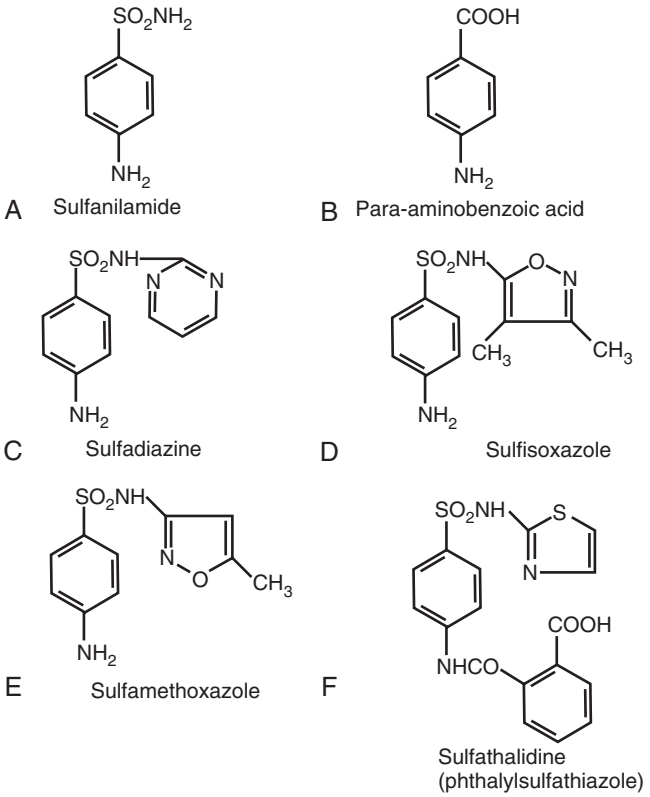


FIG. 34.1 Sulfonamides. (A–F) Structural formulas of selected sulfonamides.

peak serum level of 51 to 76 μg/mL 2.5 to 6 hours after an oral dose of 500 mg. Although resistance is noted, this combination is still used in malaria prophylaxis during pregnancy in some countries.[3]

Sulfonamides Limited to the Gastrointestinal Tract

Sulfaguanidine (*N*′-[diaminomethylene] sulfanilamide), sulfasuxidine (succinylsulfathiazole [4′-{2-thiazolylsulfamoyl}] succinanilic acid), and sulfathalidine (phthalylsulfathiazole [4′-{2-thiazolylsulfamoyl}] phthalanilic acid) are relatively poorly absorbed from the gastrointestinal tract. They have been used in the past to suppress the susceptible bowel flora before surgery. Salicylazosulfapyridine (sulfasalazine, Azulfidine) is a sulfonamide derivative used to treat ulcerative colitis. This drug is absorbed in its parent form as sulfapyridine, and significant blood levels of this compound are measurable.

Topical Sulfonamides

Mafenide acetate (para-aminomethylbenzene sulfonamide) is available for use in the topical treatment of burns. Its use has been limited, however, by metabolic acidosis caused by carbonic anhydrase inhibition. Silver sulfadiazine has fewer side effects and is used for burns,[4] although other silver compounds are being introduced.[5] In these formulations, the sulfonamide acts primarily as a vehicle for release of silver ions that exert an antibacterial effect. Outbreaks of silver-resistant infections in burn units ultimately may limit its usefulness.[6] Various combinations of other sulfonamides are available as vaginal creams or suppositories. A variety of ophthalmic ointments and solutions of sulfacetamide sodium USP (a highly soluble sulfonamide) are available for use in the treatment of conjunctivitis caused by susceptible bacteria and as adjunctive therapy for trachoma. Sulfacetamide is also used as an antiinflammatory and antimicrobial agent in the treatment of acne, rosacea, and seborrheic dermatitis.

Mechanisms of Action

Although a wide variety of chemical modifications of the sulfonamides have been synthesized, all basically share the same mechanism of action. The sulfonamides are bacteriostatic in that they inhibit bacterial growth by interfering with microbial folic acid synthesis. More specifically, sulfonamides inhibit competitively the incorporation of PABA into tetrahydropteroic acid,[7] and they may be incorporated into dihydropteroate.[8] Sulfonamides may have a higher affinity for the microbial enzyme tetrahydropteroic acid synthetase than the natural substrate PABA. Richmond[9] suggested that sulfonamides may act on bacterial repressor genes or by feedback inhibition to decrease formation of new enzymes. The ultimate result of decreased folic acid synthesis is a decrease in bacterial nucleotides, with subsequent inhibition of bacterial growth.

Antimicrobial Activity in vitro

Sulfonamides exhibit in vitro inhibitory activity against a broad spectrum of gram-positive and gram-negative bacteria; *Mycobacterium, Actinomyces, Chlamydia, Plasmodium,* and *Toxoplasma* species; and some fungi. Sulfamethoxazole is also active against *Acanthamoeba* strains.[10] The in vitro antimicrobial sensitivity of sulfonamides is influenced strongly by the size of the inoculum and the composition of the test medium. High concentrations of PABA and thymidine inhibit sulfonamide activity.

Antimicrobial Resistance

Resistance to sulfonamides is widespread and increasingly common in community-acquired and nosocomial strains of bacteria, including streptococci, staphylococci, Enterobacteriaceae, *Neisseria* spp., and *Pseudomonas* spp. Cross-resistance among different sulfonamides is common. In recent decades, sulfonamide resistance in Enterobacteriaceae and gram-positive bacteria has increased substantially.[11,12,13]

Organisms may develop point mutations in the *folP* gene, which encodes a structural change in dihydropteroate synthetase that produces an enzyme with lowered affinity for sulfonamide. The PABA binding site may be altered by F28L/T and P64S mutations in *Escherichia coli.* PABA overproduction has been implicated in resistant strains of *Neisseria gonorrhoeae* and *Staphylococcus aureus.*[14] Resistance also may be mediated by integrons that carry *sul1, sul2,* and *sul3* genes, which code for the production of drug-resistant enzymes, such as dihydropteroate synthetase, or by plasmids that decrease bacterial cell permeability to sulfonamides.[15] Plasmid transfer can occur in the gastrointestinal tract in vivo and has been seen with multiple species of Enterobacteriaceae.[16]

Transformational exchanges of dihydropteroate synthetase among *Neisseria* spp. raise the specter of wider dissemination of sulfonamide resistance by chromosomal and plasmid genes. More than one resistance mechanism may be operating simultaneously.[17]

Plasmid-mediated sulfonamide resistance in diverse species has increased greatly in recent years, often in conjunction with trimethoprim resistance. The majority of *Salmonella* isolates from human or animal origin are resistant to sulfonamides, often in conjunction with resistance to other antibiotic classes. The presence of the *sul2* gene is responsible for high-level sulfonamide resistance among *Shigella* isolates in Latin America. A US survey showed that 32% of 1118 *Shigella* isolates were sulfonamide resistant, as are more than 75% of isolates in China.[12,18] The increase in sulfonamide-resistant *Haemophilus ducreyi* in Asia and Africa has been associated with a plasmid related to those found in Enterobacteriaceae.[19] Bacterial resistance to sulfonamides has increased among human immunodeficiency virus (HIV)–infected patients during the era of increased use of TMP-SMX prophylaxis.

Pharmacology

Routes of Administration

Sulfonamides are usually administered orally. Sulfacetamide is available as a topical cream, ointment, or lotion and in ophthalmic preparations; silver sulfadiazine and mafenide acetate are applied topically in burn patients and are associated with significant percutaneous absorption of sulfonamide. Vaginal preparations are available for topical application.

Absorption

Most of the short-acting and medium-acting sulfonamides are absorbed rapidly and almost completely in the nonionized state from the small intestine and stomach. Compounds with *N*-1 substitutions are absorbed poorly, as are more acidic compounds (e.g., phthalylsulfathiazole; see

TABLE 34.1 Blood Levels, Cerebrospinal Fluid Levels, Plasma Half-Life, and Protein Binding of Some Sulfonamides

DRUG	PEAK BLOOD LEVEL[a] (mg/mL)	LEVEL IN CSF (%)	PLASMA HALF-LIFE (hr)	PROTEIN BINDING (%)
Sulfadiazine	30–60	40–80	17	45
Sulfisoxazole	40–50	30–50	5–6	92
Sulfamethoxazole	80–100	25–30	11	70
Sulfadoxine	50–75	20–30	100–230	80–98

[a]Approximate free sulfonamide level after a 2-g oral dose.
CSF, Cerebrospinal fluid.

Fig. 34.1F). Topical sulfonamides are absorbed and may be detectable in blood.

Distribution

The sulfonamides are generally well distributed throughout the body, entering the cerebrospinal fluid and synovial, pleural, and peritoneal fluids with concentrations approaching 80% of serum levels. Blood and tissue levels are related to the degree of protein binding (Table 34.1) and lipid solubility. Sulfonamides administered in pregnancy readily cross the placenta and are present in the fetal blood and amniotic fluid.

Metabolism and Excretion

Acetylation and glucuronidation occur in the liver, and free and metabolized drug appears in the urine. Glomerular filtration is probably a route of excretion, although partial reabsorption and active tubular secretion are also involved, especially at low creatinine clearance rates. Urinary excretion is more rapid for sulfonamides with low pK_a values (e.g., sulfamethizole, sulfisoxazole), and alkalinization of the urine increases excretion by this route. Plasma half-lives vary widely; they are related inversely to lipid solubility and directly to pK_a values but are not related clearly to the degree of protein binding. Small amounts of sulfonamides are found in bile, human milk, prostatic secretions, saliva, and tears.[20]

Sulfamethoxazole is primarily metabolized by the CYP2C9 hepatic enzyme system, but also by CYP3A4, and the substrate inhibits the activity of CYP2C9.[21] Excretion may be decreased in older patients, especially those with decreased creatinine clearance. Sulfadoxine half-life and area under the concentration-time curve (AUC) are reduced and clearance is increased during pregnancy.[22]

Protein Binding and Blood or Tissue Levels

Sulfonamides are bound variably and not irreversibly to plasma albumin, and the bound drug is inactive (see Table 34.1). Levels obtainable in cerebrospinal fluid and other body fluids are related inversely to the degree of protein binding. The amount of free drug in plasma is related directly to the pK_a.

Toxicity and Adverse Reactions

Sulfonamides can cause nausea, vomiting, diarrhea, rash, fever, headache, depression, jaundice, hepatic necrosis, drug-induced lupus,[23] and a serum sickness–like syndrome. Sulfadiazine used in excessively high doses is associated with crystalluria and tubular deposits of sulfonamide crystals. These complications can be minimized by maintenance of high urine flow and alkalinization of the urine. Tubular necrosis, interstitial nephritis, and necrotizing angiitis may be associated rarely with sulfonamide sensitivity.

More serious adverse reactions caused by sulfonamides may include acute hemolytic anemia sometimes related to a deficiency in erythrocyte glucose-6-phosphate dehydrogenase (G6PD), aplastic anemia, agranulocytosis, thrombocytopenia, and leukopenia.

Sulfonamides administered during the last month of pregnancy compete for bilirubin-binding sites on plasma albumin and may increase fetal blood levels of unconjugated bilirubin, increasing the risk of kernicterus. Also, because of the immature fetal acetyltransferase system, blood levels of free sulfonamide may be increased, further adversely affecting the risk of kernicterus.

Significant hypersensitivity reactions can occur with sulfonamides administered via any route. The most important of these reactions are erythema nodosum, erythema multiforme (including Stevens-Johnson syndrome), fixed-drug eruption, vasculitis similar to periarteritis nodosa, and anaphylaxis. One report suggested that cutaneous reactions, including toxic epidermal necrolysis, may be related to an inherited constitutional defect in detoxification of metabolites.[24] Locally applied sulfonamides (e.g., to skin) may be associated with any of these adverse reactions.

Many HIV-infected patients who have adverse reactions to sulfa drugs can be desensitized by gradual dose escalation or may tolerate rechallenges without severe adverse reactions.[25] Patients who are not desensitized successfully to sulfa drugs have tolerated the changing of their regimen to dapsone, with or without pyrimethamine.

Drug Interactions

Sulfonamides may displace from albumin-binding sites drugs such as warfarin, increasing the effective activity of the displaced drug. Anticoagulant dosage should be reduced during sulfonamide therapy. Sulfonamides also displace methotrexate from its bound protein, increasing methotrexate toxicity. An increased hypoglycemic effect of chlorpropamide and tolbutamide may occur during sulfonamide therapy, possibly because of the same mechanism or structural similarities. Sulfonamides may compete for binding sites with some anesthetic agents such as thiopental, and reduced barbiturate doses might be necessary. Sulfonamides may potentiate the action of some thiazide diuretics, phenytoin, and uricosuric agents. Conversely, sulfonamides themselves can be displaced from binding sites by indomethacin, phenylbutazone, salicylates, probenecid, and sulfinpyrazone, resulting in increased sulfonamide activity. Cyclosporine levels may be reduced by sulfonamides. Oral contraceptive failure during sulfonamide therapy has been noted rarely.[26]

The activity of sulfonamides may be decreased by procaine and other local anesthetics derived from PABA. Methenamine compounds should not be used with sulfonamides because of the formation of insoluble urinary precipitates. Sulfonamides may decrease protein-bound iodine and iodine 131 (^{131}I) uptake and may produce false-positive Benedict test results for urine glucose and false-positive sulfosalicylic acid test results for urine proteins.

Major Clinical Uses

Sulfonamides have been used frequently in the treatment of acute urinary tract infections. Increasing resistance has diminished their effectiveness. Because of widespread resistance of uropathogenic *E. coli,* the choice of therapy should be based on community prevalence of susceptible infecting organisms (see Chapter 72).[27]

Sulfonamides are effective for the treatment of infections caused by *Nocardia asteroides* and other *Nocardia* species, although resistance may be increasing.[28] Therapy must include 4 to 6 g or more daily after a loading dose of 4 g and should be continued for 4 to 6 months or longer, if necessary (see Chapter 253). Sulfonamides may be useful in combination with antimycobacterial drugs for the management of infections caused by some atypical mycobacteria (see Chapter 252).

Sulfonamides have been used to treat toxoplasmosis in patients with or without acquired immunodeficiency syndrome (AIDS) and chloroquine-sensitive or chloroquine-resistant *Plasmodium falciparum* malaria (with pyrimethamine). Studies have found that sulfadoxine-pyrimethamine

malaria prophylaxis is well tolerated in pregnant women,[3] but increased resistance has been reported. The optimal treatment for toxoplasmic encephalitis is the combination of pyrimethamine plus sulfadiazine or, for patients intolerant to sulfonamides, pyrimethamine plus clindamycin. In most studies, both regimens seem equally efficacious.[29] The pyrimethamine-sulfadiazine regimen begins with a 4- to 8-week induction course of pyrimethamine (100–200 mg once daily for 1 day, followed by 50–75 mg once daily) plus sulfadiazine (1–2 g four times daily). Leucovorin (5–50 mg once daily) is administered to prevent pyrimethamine-associated folinic acid deficiency. Sulfadiazine may be given twice daily (2 g), even during induction therapy.[30] Sulfonamide desensitization has been effective for patients with cerebral toxoplasmosis and allergies to sulfonamides. High-dose TMP-SMX (see later) is an effective alternate for AIDS-related cerebral toxoplasmosis, although pyrimethamine-sulfadiazine has been considered preferable.[29] Melioidosis, dermatitis herpetiformis, lymphogranuloma venereum, and chancroid have responded to sulfonamides. Nongonococcal urethritis caused by *Chlamydia,* but not caused by *Ureaplasma urealyticum,* responded to sulfonamide therapy (see Chapters 180 and 184). Sulfasalazine is used in the treatment of inflammatory bowel diseases.[31] Currently, sulfonamides are used most frequently in combination with trimethoprim (see later). Sulfamethoxazole at 800 mg dosing might have a future role in the treatment of multidrug-resistant (MDR) tuberculosis.[32]

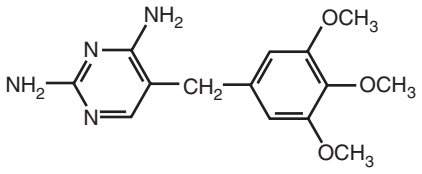
TRIMETHOPRIM

Structure and Derivation

Trimethoprim is a 2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl) pyrimidine (Fig. 34.2). This drug was synthesized by Bushby and Hitchings[2] as a DHFR inhibitor thought to potentiate the activity of sulfonamides by sequential inhibition of folic acid synthesis. In the United States, trimethoprim is available as a single agent and in combination with sulfamethoxazole (co-trimoxazole; see later). Trimethoprim has antibacterial activity of its own.

Mechanism of Action

Trimethoprim owes its activity to powerful inhibition of bacterial DHFR, which is the next enzymatic step after folic acid synthesis is blocked by sulfonamides. Trimethoprim is 50,000 to 100,000 times more active against bacterial DHFR than against the human enzyme. Trimethoprim interferes with the conversion of dihydrofolate to tetrahydrofolate, the precursor of folinic acid and ultimately of purine and DNA synthesis (Fig. 34.3). The sequential blockage of the same biosynthetic pathway by sulfonamides and trimethoprim results in a high degree of synergistic activity against a wide spectrum of microorganisms. Humans do not synthesize folic acid but require it in their diet, and human purine synthesis is not affected significantly by the enzyme inhibition of trimethoprim.[33]



(2,4-diamino-5-[3′,4′,5′-trimethoxybenzyl] pyrimidine)

FIG. 34.2 Chemical structure of trimethoprim.

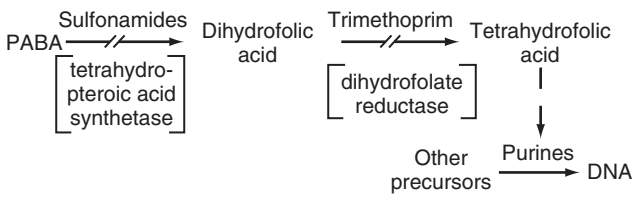


FIG. 34.3 Action of sulfonamides and trimethoprim on the metabolic pathway of bacterial folic acid synthesis. *DNA,* Deoxyribonucleic acid; *PABA,* para-aminobenzoic acid.

Antimicrobial Activity

Trimethoprim is active in vitro against many gram-positive cocci and most gram-negative rods, except for *Pseudomonas aeruginosa* and *Bacteroides* spp. *Treponema pallidum, Mycobacterium tuberculosis, Mycoplasma* spp., and most anaerobes are resistant. Thymidine inhibits the in vitro activity of trimethoprim, but the addition of thymidine phosphorylase or 5% lysed horse blood, which releases the phosphorylase to Mueller-Hinton medium or other sensitivity media, removes this inhibition. The minimal inhibitory concentration (MIC) varies considerably with the medium used. Trimethoprim alone has good in vitro activity against *H. influenzae*; a survey has shown that 76% of 978 strains remain susceptible, but higher resistance rates are reported elsewhere.[34] *Streptococcus pyogenes* MICs have been reported at less than or equal to 2 μg/mL,[35] but several transferable genes mediating resistance to trimethoprim are increasingly common and limit usefulness against these organisms.[36]

Resistance to Trimethoprim

Clinical resistance to trimethoprim is increasing and may be due to selection of bacterial cells with altered permeability, loss of drug-binding capacity, overproduction of or alterations in DHFR, or a combination of these factors. A decrease in the ratio of strains resistant to sulfamethoxazole and trimethoprim compared with strains resistant only to trimethoprim may reflect an increase in independent trimethoprim resistance, which might be a useful monitoring parameter in hospitals.[37]

Clinically, the most important mechanism is plasmid-mediated DHFRs that are resistant to trimethoprim.[38] Distinctive DHFRs mediated by *dfr* genes have been described in Enterobacteriaceae, *P. aeruginosa, H. influenzae, Streptococcus pneumoniae, S. aureus,* and *Campylobacter* spp. that may be chromosomally resistant to high trimethoprim concentrations. These resistant enzymes often may be plasmid mediated and disseminated by highly mobile transposons (e.g., Tn7) with wide host species ranges. Outbreaks caused by trimethoprim-resistant conjugative plasmids have been noted in multiple centers in Europe, Asia, and the Americas.[39] Many of the outbreaks occurred in immunocompromised hosts, with organisms manifesting resistance to multiple other antibiotic groups. DHFR variants in *P. jiroveci* pneumonia isolates may be associated with resistance to TMP-SMX.[40]

Variable local increases in trimethoprim resistance, particularly among Enterobacteriaceae, have been reported. Recent surveys have found trimethoprim resistance steadily increasing among *E. coli* uropathogens.[41] Whether the clinical use of trimethoprim alone in some countries has resulted in increasing resistance to TMP-SMX is unclear.

Pharmacology

Routes of Administration

Trimethoprim is available as 100-mg tablets for oral use. Trimethoprim is absorbed readily and almost completely from the gastrointestinal tract. Peak serum levels appear 1 to 4 hours after ingestion of 100 mg and approach 1 μg/mL. The coadministration of sulfamethoxazole does not affect the rate of absorption or serum levels of trimethoprim.

Distribution

Trimethoprim is distributed widely in tissues and may appear in kidney, lung, and sputum in higher concentrations than in plasma and in bile, saliva, human breast milk, and seminal fluid.[42] Trimethoprim is also found in prostatic fluid at two to three times the serum concentration, but lower levels may be present in patients with chronic prostatitis. Cerebrospinal fluid concentrations are about 40% of serum levels.

Metabolism and Excretion

Approximately 60% to 80% of an administered dose of trimethoprim is excreted in the urine via tubular secretion within 24 hours. The remainder of the drug is excreted by the kidney in one of four oxide or hydroxyl derivatives. The urinary metabolites are bacteriologically inactive.[43] Trimethoprim is also a major substrate of CYP2C9 and a minor substrate of CYP3A4. Its metabolism inhibits CYP2C8 and CYP2C9.[21] Trimethoprim is also excreted in the bile. The serum half-life ranges from 9 to 11 hours in healthy subjects and is prolonged in patients

with renal insufficiency. In contrast to sulfamethoxazole, the excretion rate of trimethoprim is increased with acidification of the urine, and serum protein binding (65%–70%) does not decrease significantly with increasing degrees of uremia. Urine concentrations in healthy subjects (60–1000 μg/mL) are usually greater than the MIC of many urinary pathogens.

Clinical Use

The primary use of trimethoprim alone is in the prevention of recurrent uncomplicated urinary tract infections in women with structurally normal anatomy.[44] Trimethoprim has been successful in the treatment of acute urinary tract infections at a dose of 100 mg twice daily,[45] but increasing resistance threatens its usefulness.[38]

TRIMETHOPRIM-SULFAMETHOXAZOLE

Mechanism of Action and Antimicrobial Activity

Potentiation of the action of trimethoprim is seen in combination with sulfamethoxazole in a ratio of 1:5 for oral use (trimethoprim, 80 mg; sulfamethoxazole, 400 mg). Double-strength and quarter-strength pediatric tablets are available, as is an oral suspension containing 40 mg of trimethoprim and 200 mg of sulfamethoxazole per 5 mL. Intravenous (IV) trimethoprim (16 mg/mL) plus sulfamethoxazole (80 mg/mL) is available. When administered intravenously, 10 mL or 160 mg of trimethoprim (with 800 mg of sulfamethoxazole) produces a peak serum trimethoprim concentration of 3.4 μg/mL in 1 hour. After repeated doses, the peak trimethoprim concentration may approach 9 μg/mL.[43] Similar peak levels may be reached with oral therapy, but at 2 to 4 hours after administration.[46]

The combination of trimethoprim and sulfamethoxazole (TMP-SMX, co-trimoxazole) is active in vitro against many isolates of *S. aureus,* including many community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains, but because of local variations, susceptibility testing should be performed. Dissemination of trimethoprim resistance in MRSA via the *dfrG* gene from Africa to Europe has been reported.[47] In vitro TMP-SMX activity is reported for *S. pyogenes, S. pneumoniae* (although resistance is increasing in patients receiving TMP-SMX prophylaxis[48]), *Moraxella catarrhalis, E. coli, Proteus mirabilis, Burkholderia cepacia, Burkholderia pseudomallei,*[49] *Yersinia enterocolitica* (but resistance has been reported), *N. gonorrhoeae* (resistance rates higher than 20% reported[50]), and *Stenotrophomonas maltophilia.* TMP-SMX–resistant strains of *S. maltophilia,* often mediated by one of several circulating integrons, are increasing and may occur in severely ill patients with serious morbidity.[51,52] Of pneumococci carried in the nasopharynx of children treated for malaria with a sulfonamide or TMP-SMX, 50% were resistant to TMP-SMX.[53] A study from Finland has documented an increasing prevalence of TMP-SMX resistance in *S. pneumoniae, M. catarrhalis,* and *H. influenzae* and found that regional use of TMP-SMX was associated with increasing resistance among pneumococci.[54] Variable TMP-SMX resistance has been reported in penicillin-susceptible and penicillin-nonsusceptible pneumococci.[55] A large Finnish study of more than 20,000 *S. pneumoniae* isolates correlated TMP-SMX resistance with increasing use.[56] A more recent study among HIV-infected South African patients with invasive pneumococcal infections reported that TMP-SMX prophylaxis was associated with pneumococcal nonsusceptibility to TMP-SMX, in addition to rifampin and penicillin.[48] The Etest might not be reliable for the determination of TMP-SMX–resistant pneumococci. A wide range of TMP-SMX susceptibilities among *Salmonella* and *Shigella* spp. has been reported; for example, 80% of *Shigella* isolates from Shanghai were resistant,[18] as were 90% in Bangladesh.[57]

Variable bactericidal effects have been noted when enterococci are tested against TMP-SMX, but TMP-SMX is not clinically useful. However, one report suggested that standard in vitro testing might not predict clinical outcome and might underestimate the effectiveness of trimethoprim alone in enterococcal urinary tract infections.[58] The susceptibility of Enterobacteriaceae may vary greatly among locations and within the same location from year to year because of the spread of trimethoprim-resistant plasmids and transposons. Almost all strains of *P. aeruginosa* are resistant in vitro to TMP-SMX.

Trimethoprim combined with sulfamethoxazole or dapsone has been effective in the treatment of *Pneumocystis jiroveci* pneumonia in immunocompromised patients (see later). *Listeria monocytogenes, M. catarrhalis,* and atypical mycobacteria have been shown to be susceptible to TMP-SMX, but variable rates of resistance are reported.

The optimal ratio for in vitro synergism of TMP-SMX in combination is 1:20, but this ratio does not always apply in vivo. The synergism seen depends on the sensitivity of the organism to each drug.

Trimethoprim-Sulfamethoxazole Resistance

Concomitant trimethoprim and sulfonamide resistance may limit the usefulness of TMP-SMX against some strains of MRSA and *Staphylococcus epidermidis.* The most commonly circulating CA-MRSA clone (USA300) often has been susceptible to TMP-SMX,[59] but increasing levels of TMP-SMX resistance have been reported in European isolates.[60] In HIV-infected patients, TMP-SMX use has been associated with TMP-SMX resistance among *S. aureus* and Enterobacteriaceae,[61] with recent increases in resistance documented in respiratory and urinary isolates.[62] Until recently, there was limited evidence that TMP-SMX selects for resistance to other antibiotic classes.[63] However, more recent studies have suggested that multiple drug resistance is common now in *E. coli* isolated from the urinary tract, with TMP-SMX resistance rates approaching 25% in the United States.[64] *E. coli* carrying extended-spectrum β-lactamases may have concomitant high rates of resistance to TMP-SMX (65% in one study[65]), which are often plasmid mediated. Patients with *E. coli* urinary tract infections caused by the 025b/ST131 clone are less likely to respond to TMP-SMX, and the related MDR ST131-H30R1 and ST1131-H30Rx strains are becoming more widely disseminated.[66,67]

Permeability changes may occur in the bacterial cell and result in resistance to trimethoprim and sulfonamides. Thymine-requiring auxotrophs may also account for clinically significant resistance to both drugs. These mutants lack thymidylate synthetase and are probably less virulent than sensitive strains.[38] Many *Shigella* spp. are resistant to TMP-SMX, mediated by several different integrons.[57,68,69] TMP-SMX resistance is increasing among many *Salmonella* spp., with international travel potentiating spread.[70] Except for strains originating in Southeast Asia, many *Salmonella* Typhi strains retain susceptibility.[71] However, multiclass plasmid-mediated resistance, including TMP-SMX resistance, has been reported in *Salmonella enterica.* A widely disseminated integron has been associated with high levels of TMP-SMX resistance in multiple species of Enterobacteriaceae.[72] Resistance is also increasing in *Acinetobacter baumannii* strains.[73] *P. jiroveci* may also develop sulfonamide and trimethoprim resistant mutations in the course of therapy of immunocompromised HIV-infected patients, resulting in treatment failure.[74]

Metabolism and Excretion

TMP-SMX can be given in the usual doses to patients with a creatinine clearance of 30 mL/min or higher. One half of the usual daily dose can be given to patients with a creatinine clearance of 15 to 30 mL/min, but TMP-SMX is not recommended for use in patients with a creatinine clearance lower than 15 mL/min.[75] Trimethoprim and nonacetylated sulfamethoxazole are removed by hemodialysis. Patients needing long-term peritoneal dialysis can be given the equivalent of one double-strength TMP-SMX tablet every 48 hours.

Toxicity and Side Effects

The toxic and undesired effects of TMP-SMX include all the effects discussed previously for sulfonamides. Nausea, vomiting, diarrhea, anorexia, and hypersensitivity reactions are the most common.[76]

Dermatologic Reactions

Rash and other adverse reactions, including hypouricemia (after high-dose therapy)[77] and Sweet syndrome (acute febrile neutrophilic dermatosis), have been noted frequently in patients with AIDS, in whom adverse reactions to TMP-SMX appear more frequently than in other patients.[78] The pathophysiology of sulfonamide hypersensitivity associated with HIV infection is multifactorial and probably relates to a number of metabolic, immunologic, host-related, and viral factors.[79–81] HIV-associated T-cell dysfunction[79,80] and major histocompatibility complex

(MHC)–dependent drug presentation[81] likely contribute to these effects. Toxic epidermal necrolysis and Stevens-Johnson syndrome may occur in 1 to 2 per 1000 treated individuals.[82] Patients have been desensitized successfully with the use of oral regimens.[29] Other dermatologic manifestations, including exanthems, fixed drug eruptions, baboon syndrome, erythrodermic psoriasis, and nail loss, have been reported. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) also may occur.[83]

Hematologic Reactions

In addition, impaired folate use may be seen in humans with prolonged administration. This usually manifests as a megaloblastic marrow, with hypersegmented polymorphonuclear leukocytes. Methemoglobinemia (neonatal) and leukopenia, thrombocytopenia, and granulocytopenia or agranulocytosis may be seen with fatal results.[76,84] Hypoprothrombinemia and drug-induced thrombocytopenia have been reported.[76] The administration of folinic acid usually prevents or effectively treats the antifolate effects of trimethoprim, and trimethoprim's antibacterial efficacy is not impaired, except possibly against enterococci.

Renal and Electrolyte Abnormalities

Renal dysfunction may occur in patients with preexisting renal disease, but this is reversible with dose reduction. Hyponatremia, hypernatremia, and hyperkalemia have been noted, especially after high doses and in patients with renal insufficiency.[76] The incidence of TMP-SMX–induced hyperkalemia is increased in older patients, especially those treated with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and spironolactone, but not with β-blockers.[76,85] When used in combination with an angiotensin-converting enzyme inhibitor in older patients, TMP-SMX was associated with an elevated risk of sudden death compared with amoxicillin and other antibiotics.[86,87] Interstitial nephritis attributable to TMP-SMX has been described, especially in transplant recipients[88] and patients with AIDS. Lactic acidosis may occur, and although renal tubular acidosis is uncommon,[89] it has been reported in children undergoing treatment for acute lymphocytic leukemia.

Gastroenterologic and Hepatic Effects

Pseudomembranous colitis has been described with TMP-SMX but is uncommon, possibly because the effect of the drugs on the predominantly anaerobic colonic microbiota is low. Drug-induced, dose-dependent cholestasis and hepatocellular injury, especially severe in African Americans and in HIV-infected patients, have been reported,[90,91,92] and prolonged cholestasis with pruritus may occur rarely. Pancreatitis[93] and fulminant hepatic failure have also been reported, especially in liver transplant patients.[94] The incidence of hepatotoxicity may be decreased in patients receiving concomitant fluconazole because it can decrease tissue TMP-SMX levels.

Neurologic and Psychiatric Effects

TMP-SMX–induced meningoencephalitis and aseptic meningitis have been described.[76] Although other central nervous system effects are seen primarily in HIV-infected patients, tremor and gait disturbances have been reported.[76] Acute psychosis and hallucinations associated with TMP-SMX treatment have been reported.[95,96]

Miscellaneous Adverse Effects

Drug-induced hypoglycemia may occur, especially in combination with sulfonylureas,[76,97] and rhabdomyolysis has been described in an HIV-infected patient.[98] Acute parotitis may occur.[99] Anterior uveitis and retinal hemorrhage have been described with trimethoprim alone and with TMP-SMX, as have reversible myopia and angle-closure glaucoma. In patients with AIDS, anaphylactoid reactions and transient diffuse pulmonary infiltrates with hypotension have been described after reexposure to TMP-SMX. TMP-SMX–induced acute fibrinous organizing pneumonia has been described.

Antiphospholipid antibody syndrome may occur.[100] TMP-SMX is associated with an increased risk of fetal abnormalities,[101] low birth weight, and preterm delivery.[102] Anti-ribonucleoprotein (RNP) antibodies or genetic polymorphisms may predict TMP-SMX hypersensitivity and adverse events.[103,104]

TABLE 34.2 Clinically Relevant Drug Interactions With Trimethoprim (TMP) and Sulfamethoxazole (SMX)

Drugs That May Increase TMP-SMX Levels
Carbamazepine
Phenobarbital
Phenytoin
Rifampin
Rifapentine
Secobarbital
Drugs Used With TMP-SMX That May Result in Toxicity
Amantadine (delirium)
Angiotensin-converting enzyme inhibitors (hyperkalemia)
Angiotensin receptor antagonists (hyperkalemia)
Cyclosporine (nephrotoxicity)
Methotrexate (anemia)
Pyrimethamine (anemia)
Sulfonylureas (hypoglycemia)
Warfarin (hypoprothrombinemia and bleeding)
Drugs With Which TMP-SMX May Increase Drug Levels
Amiodarone
Bosentan
Dapsone
Fluoxetine
Glimepiride
Glipizide
Losartan
Montelukast
Nateglinide
Paclitaxel
Phenytoin
Pioglitazone
Repaglinide
Rifampin
Rosiglitazone
Warfarin
Zafirlukast

Modified from Wen X, Wang JS, Backman JT, et al. Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. Drug Metab Dispos. *2002;30:631–635.*

Drug Interactions

Drug-drug interactions occur; the major interactions are summarized in Table 34.2.[21] TMP-SMX interacts with warfarin through the CYP450, CYP2C9 system, increasing bleeding risk.[105] Active levels of phenytoin may be increased markedly by TMP-SMX, especially in elderly patients.[106] Also, concomitant administration of TMP-SMX and methotrexate results in decreased renal clearance of free methotrexate, and severe or even fatal pancytopenia may result.[107] Reversible inhibition of tubular creatinine excretion may be caused by trimethoprim in the presence of cyclosporine,[21] but TMP-SMX did not affect sirolimus pharmacokinetics in a study of renal transplant recipients.[108] Digoxin levels may be increased, and sulfonylureas may be potentiated with resulting hypoglycemia. Serum rifampin levels may increase during concomitant therapy with TMP-SMX.[21] Older patients treated with concomitant TMP-SMX and spironolactone are at increased risk for sudden death.[109] Although TMP-SMX may inhibit the metabolism of some antiretroviral drugs, including lamivudine and saquinavir, the effect is minimal and does not require adjustment of antiretroviral drug dosage.

Trimethoprim Plus Other Antimicrobial Agents

Other sulfonamides, such as sulfamoxole, sulfadiazine, sulfadimidine, and sulfametrole, have been combined with trimethoprim, but clinical experience is limited. Although combinations of trimethoprim with other agents, such as rifampin, polymyxin, amikacin, and metronidazole, have been studied, extensive clinical experience with these combinations is lacking. A randomized controlled trial of HIV-infected patients with mild-to-moderate *P. jiroveci* pneumonia found that trimethoprim-dapsone was comparable with TMP-SMX in terms of overall activity and tolerability.[110] Because it is the least expensive and most carefully studied

regimen, TMP-SMX continues to be first-line therapy for HIV-associated *P. jiroveci* pneumonia.

Clinical Uses of Trimethoprim-Sulfamethoxazole

The increasing worldwide rates of TMP-SMX resistance have seriously limited the clinical usefulness of co-trimoxazole and its components.

Urinary Tract Infections

TMP-SMX is useful in the treatment of recurrent or chronic urinary tract infections caused by susceptible organisms. The combination is effective for acute pyelonephritis and cystitis (see Chapter 72), although either antibiotic alone could be appropriate for susceptible isolates. Recent reports have cautioned against their routine use if rates of resistance approach 20%, as they currently do in several populations.[41,65,111] Because trimethoprim accumulates in prostatic secretions, TMP-SMX is often effective in bacterial prostatitis and in orchitis and epididymitis caused by susceptible bacteria, and is frequently used after transurethral prostate biopsy.

The usual adult dosage for the treatment of acute prostate or urinary infection is two tablets every 12 hours or one double-strength tablet every 12 hours. The pediatric dose for urinary tract infection is 150 to 185 mg/m^2 for trimethoprim and 750 to 925 mg/m^2 for sulfamethoxazole daily in two divided doses. Single-dose therapy with one or two double-strength tablets may be effective in some women with uncomplicated lower urinary tract infection, but longer-term therapy is usually necessary in patients with complicated urinary tract infections (see Chapter 72).

TMP-SMX has been shown to be useful in the long-term suppressive therapy of adults and children with chronic or recurrent urinary infections, and extremely low doses (one-half to one tablet at bedtime or every other night) may still be effective. This approach has been useful in preventing recurrent urinary tract infections in children with vesicoureteral reflux, although long-term outcomes were no different with or without prophylaxis.[112] A recent study found that although children receiving TMP-SMX prophylaxis to prevent recurrent urinary tract infections were more likely to develop resistant isolates, their rates of recurrence did not differ from the rates in those who did not receive prophylaxis.[113] Postcoital prophylactic TMP-SMX may reduce recurrent urinary tract infections related to intercourse. Trimethoprim achieves effective concentrations in the vaginal secretions, and it might exert a protective effect on reducing the number of recurrent infections despite the fact that TMP-SMX–resistant organisms may be present in the vaginal and stool flora.[114] As mentioned earlier, trimethoprim alone is effective therapy for uncomplicated and recurrent urinary tract infections in women. Usual doses are 100 to 200 mg twice daily, and nightly doses of 100 mg may be effective suppressive therapy. Increasing rates of trimethoprim and TMP-SMX resistance should minimize the widespread empirical use of these drugs, unless bacterial susceptibility is known.[27,114]

Respiratory Tract Infections

TMP-SMX is effective in the treatment of acute bronchitis and pneumonitis caused by sensitive organisms, although it is not the treatment of choice for any single organism. Previously, TMP-SMX was as effective as tetracyclines in the reduction of acute exacerbations in patients with chronic bronchitis, but more recent studies have show equivalent results with TMP-SMX compared with ciprofloxacin.[115]

TMP-SMX was effective for the treatment of otitis media, otitis externa, and sinusitis. However, a later report strongly suggested that TMP-SMX no longer be used as first-line therapy for acute otitis media, especially when resistant respiratory tract pathogens predominate.[116] Ampicillin-resistant strains of *H. influenzae* and *M. catarrhalis* might or might not be susceptible.

Gastrointestinal Infections

Although antibiotics per se prolong the carrier state in acute gastroenteritis caused by *Salmonella* spp., TMP-SMX was effective in eliminating chronic *Salmonella* carriage, including carriage of *Salmonella* Typhi, especially in patients older than 2 years. Typhoid fever was also treated successfully with this combination, although the development of resistant strains has been reported. TMP-SMX may be effective in shigellosis, but resistance is high.[12,18] TMP-SMX also was effective in treating diarrhea caused by enteropathogenic *E. coli* and in the treatment and prophylaxis of traveler's diarrhea with or without loperamide, but increased resistance precludes its empirical use. The combination may be a useful adjunct to fluids in the treatment of cholera, but Huovinen[38] has suggested that with the exception of this possible second-line or third-line use in cholera, TMP-SMX no longer is indicated for *Salmonella, Shigella, Campylobacter,* or enterotoxigenic *E. coli* infections. Comparable efficacy with a fluoroquinolone has been reported for the prevention of spontaneous bacterial peritonitis in cirrhotics.[117]

Skin, Soft Tissue, and Bone Infections

With the increasing incidence of community-acquired methicillin-resistant staphylococcal soft tissue infections,[118] antimicrobial susceptibility testing of clinical isolates has become important. Several community-based series have documented that the vast majority of isolates from the most commonly disseminated USA300 clone are susceptible to TMP-SMX.[47,119] Several studies have suggested that oral TMP-SMX in combination with prompt incision and drainage of fluctuant lesions can result in rapid resolution of infections that, if untreated, can result in bacteremia, pyomyositis, and other severe complications.[120] Two recent studies showed that TMP-SMX (or clindamycin) results in improved outcomes after incision and drainage for uncomplicated skin or subcutaneous abscesses due to MRSA.[121,122] TMP-SMX may be useful in cellulitis, impetigo,[123] acne vulgaris,[124] and head lice (with topical permethrin).[125] TMP-SMX plus rifampin may be as effective as linezolid in chronic MRSA osteomyelitis, and oral TMP-SMX was reported to be effective in the treatment of acute osteomyelitis in children.[126]

Sexually Transmitted Diseases

Historically, TMP-SMX had been effective in the treatment of uncomplicated gonorrhea when used in several dosage regimens (e.g., two tablets orally twice daily for 5 days, four tablets for 2 days, and a single dose of eight tablets). For pharyngeal gonorrhea, especially that caused by penicillinase-producing *N. gonorrhoeae,* nine tablets daily for 5 days was recommended previously, but these regimens no longer are included in the Centers for Disease Control and Prevention guidelines for treatment of sexually transmitted infections. TMP-SMX is ineffective for syphilis. As a result of increased resistance, TMP-SMX is no longer indicated for the treatment of gonorrhea, chancroid, or *Chlamydia trachomatis* infections.

Recent reports have documented clusters of CA-MRSA among men who have sex with men (MSM).[59] A review of personal practices has suggested that increased transmission of MRSA in MSM occurs among those with increased numbers of sexual partners, particularly if they engage in practices that abrade skin or mucous membranes. Almost all isolates from these clusters were multidrug resistant, but most were susceptible to TMP-SMX.[47]

Other Infections

TMP-SMX remains useful against brucellosis (long-term therapy for 6 weeks), but resistance is increasing. Nonetheless, a publication from Turkey reported that only 1 of 42 bacteremic isolates was resistant to TMP-SMX.[127] In combination with rifampin and a tetracycline, TMP-SMX was successful in treating *Brucella* endocarditis.[128] Sulfonamides and TMP-SMX are useful in nocardiosis, including *Nocardia* keratitis, but resistance may occur.[129] Prolonged oral TMP-SMX after 10 to 14 days of IV broad-spectrum β-lactam therapy has been successful in many cases of melioidosis, but optimal dosing should be weight based[130]; TMP-SMX alone may be as effective as in combination with doxycycline.[131] TMP-SMX may be successful in *B. cepacia* bacteremia. Trimethoprim and sulfonamides have been used successfully in Whipple disease, but genetically mediated *Tropheryma whipplei* resistance can be acquired during therapy, resulting in treatment failure.[132] Optimal outcomes were obtained with 2 weeks of IV ceftriaxone followed by 3 months of oral TMP-SMX.[133] TMP-SMX alone may result in relapse[134] and is not as effective as doxycycline plus hydroxychloroquine. TMP-SMX is used in granulomatosis with polyangiitis (GPA) alone or as adjunctive therapy and may reduce relapses.[135] TMP-SMX can be used to treat

infections caused by *Mycobacterium chelonae, Mycobacterium fortuitum,* and *Cyclospora cayetanensis*.

IV TMP-SMX has been useful in treating gram-negative rod bacteremia and staphylococcal bacteremia and endocarditis, although other agents are preferred, given the increasing resistance of Enterobacteriaceae[136] and staphylococci globally. A study showed comparable efficacy for TMP-SMX or vancomycin in the treatment of MRSA bacteremia.[137] TMP-SMX plus vancomycin has shown in vitro synergistic activity when tested against vancomycin-intermediate *S. aureus*, and TMP-SMX plus ceftaroline may be useful in MRSA bacteremia and endocarditis.[138] A TMP-SMX lock solution may prevent bloodstream infections in patients with hemodialysis catheters.

TMP-SMX has been recommended for the treatment of *S. maltophilia* bacteremia; most isolates are susceptible in vitro.[139,140,141] Outcomes have been good in patients with *S. maltophilia* lower respiratory infections who were treated with TMP-SMX. TMP-SMX plus ticarcillin-clavulanate has been used to treat *S. maltophilia* infections in patients with cancer.[142]

Meningitis caused by susceptible organisms may be treated successfully, but other agents are usually preferred. The combination is effective in meningitis caused by *L. monocytogenes,*[143] and TMP-SMX prophylaxis may prevent listeriosis in transplant recipients.[144] *Mycobacterium kansasii, Mycobacterium marinum,* and *Mycobacterium scrofulaceum* are inhibited in vitro by TMP-SMX, and several clinical successes have been reported, often in combination with other agents.[145] TMP-SMX is used in combination with isoniazid and rifampin to treat leprosy.[146]

TMP-SMX has been used in the treatment of susceptible *P. falciparum* infections, although this combination is not active against MDR strains.[147] Sulfadoxine-pyrimethamine with or without azithromycin is effective antimalarial therapy in pregnant women at delivery.[148] HIV-infected patients with *Cystoisospora belli* enteritis have had clinical responses after receiving TMP-SMX; however, relapse after treatment is common, necessitating long-term suppressive therapy.[29,149] TMP-SMX has been shown to decrease the duration of oocyst excretion in children with *C. cayetanensis* infection[149] and is more effective than ciprofloxacin in HIV-infected adults with cyclosporiasis or isosporiasis. TMP-SMX has no activity against other related coccidial parasites, such as *Cryptosporidium parvum*.

TMP-SMX is active against *Toxoplasma gondii* in vitro and has been used clinically but has not been considered superior to first-line therapy with pyrimethamine-sulfadiazine; however, a meta-analysis has suggested that clinical response and medication toxicity rates are comparable between the two regimens.[150] Also, a study has suggested comparable activity in ocular toxoplasmosis,[151] and TMP-SMX may be taken by the oral or intravitreous route; TMP-SMX plus azithromycin is also effective.[152] TMP-SMX prophylaxis in HIV-infected patients protects against toxoplasmosis and may reduce the incidence of bacterial infections.[29] TMP-SMX plus spiramycin may reduce *Toxoplasma* transmission from mother to child.[153] TMP-SMX has excellent in vitro activity against *Acanthamoeba,*[10] and two cases of *Acanthamoeba* meningitis were treated successfully with combination therapy that included TMP-SMX.[154] TMP-SMX is recommended in the management of Q fever in pregnant women[155] and is as effective as a macrolide in the eradication of nasopharyngeal *Bordetella pertussis*.[156]

Pneumocystis jiroveci Infections in HIV-Infected Patients

TMP-SMX has been highly efficacious in the treatment of *P. jiroveci* pneumonia in immunocompromised HIV-infected patients and is considered first-line therapy.[157] TMP-SMX therapy for HIV-infected patients with *P. jiroveci* pneumonia had been associated with a better safety and toxicity profile than trimetrexate or pentamidine and a higher survival rate than atovaquone (see also Chapter 269).[157] Other alternative agents include trimethoprim-dapsone or clindamycin and primaquine. Patients with AIDS frequently respond to therapy but have a higher incidence of adverse reactions, particularly neutropenia and rash.[29,76] Severe hyponatremia and hyperkalemia have also been described. TMP-SMX may be administered orally (two double-strength tablets every 8 hours) or intravenously (5 mg/kg of trimethoprim plus 25 mg/kg of sulfamethoxazole every 8 hours) for 3 weeks. Patients were more likely to manifest a hypersensitivity reaction while receiving TMP-SMX if they had higher $CD4^+$ T-lymphocyte counts and were treated for longer than 2 weeks, suggesting a role for intact cell-mediated immunity in the pathogenesis of these reactions. A multicenter study suggested that lower doses of TMP-SMX (<15 mg/kg of TMP per day) for *P. jiroveci* pneumonia may be comparably effective to full dosing and may result in lower levels of toxicity; another study found comparable therapeutic responses when TMP-SMX doses were decreased during the course of therapy.[158,159] Trimethoprim has also been used successfully with dapsone for treatment of mild-to-moderate *P. jiroveci* pneumonia.[110] The development of TMP-SMX resistance mutations has been associated with *P. jiroveci* treatment failures.[74] The clinical significance of *P. jiroveci* mutations has been debated; at this time there is no indication to monitor *P. jiroveci* resistance mutations prospectively.

TMP-SMX has been used successfully for primary and secondary chemoprophylaxis of *P. jiroveci* pneumonia,[29] is highly cost-effective, and is generally selected as the first-line agent, but its long-term use may be limited by toxicities such as rash or leukopenia.[76] WHO now recommends that all HIV-infected patients with a $CD4^+$ count of 350 cells/mm^3 or lower, thrush, or prior *P. jiroveci* pneumonia receive prophylaxis with TMP-SMX unless they are sulfa allergic, and that in settings with "a high burden of infectious disease," prophylaxis should be considered irrespective of CD4 count.[160] A prospective study has shown that a double-strength tablet taken every other day had comparable efficacy to daily TMP-SMX, with fewer side effects. AIDS patients receiving *P. jiroveci* prophylaxis with TMP-SMX may have fewer serious bacterial infections than patients who did not receive prophylaxis. A study from Africa showed that extending TMP-SMX prophylaxis in children with HIV decreases rates of hospitalization with malarial and nonmalarial infections,[161] consistent with the findings of other studies that HIV-infected and uninfected children receiving TMP-SMX prophylaxis had decreased rates of malaria.[162] Another study found decreased rates of *Loa loa* in patients receiving TMP-SMX prophylaxis, suggesting a possible anthelmintic effect, because the effect was not mediated by antiretroviral use.[163] TMP-SMX is comparable in tolerability and efficacy to second-line regimens, is much less expensive, and is associated with improved survival. Current guidelines suggest discontinuing primary prophylaxis for patients who have a sustained $CD4^+$ count higher than 200 cells/mm^3 for at least 3 months after the initiation of highly active antiretroviral therapy.[29] *P. jiroveci* pneumonia prophylaxis with TMP-SMX confers cross-protection against toxoplasmosis.[29] TMP-SMX is the recommended prophylactic agent for toxoplasmosis for all patients with a $CD4^+$ count lower than 100 cells/mm^3 and a previous episode of toxoplasmic encephalitis. Dapsone is an effective alternative in patients with TMP-SMX allergy. TMP-SMX prophylaxis has been lifesaving when used in immunosuppressed AIDS patients in sub-Saharan Africa and is now the standard of care.[164] TMP-SMX prophylaxis is moderately protective against malaria in HIV-exposed infants and HIV-infected children,[165] and in African children in areas with high levels of antifolate resistance.[166] HIV-infected patients who discontinue TMP-SMX prophylaxis are at increased risk of malaria and diarrhea.[167,168] TMP-SMX may be used in patients with paracoccidioidomycosis, but is not as effective as itraconazole.[169]

Trimethoprim-Sulfamethoxazole Use in Other Immunocompromised Patients

Previous evidence for a striking reduction in gram-negative rod bacteremia in neutropenic patients treated prophylactically with TMP-SMX is controversial.[170] In a more recent meta-analysis, TMP-SMX was effective in reducing gram-positive bacteremia in these patients.[171] Oral prophylaxis with TMP-SMX may decrease the incidence of serious bacterial infections in patients with multiple myeloma. Concerns have been raised about the routine use of TMP-SMX prophylaxis in neutropenic patients because of increasing streptococcal resistance.[172] TMP-SMX remains the preferred *P. jiroveci* prophylactic regimen for patients receiving chemotherapy for hematologic malignancies and for stem cell transplant recipients.[173] Effective prophylactic use of TMP-SMX in chronic granulomatous disease has been reported.[174] Twice-weekly TMP-SMX provides effective *Pneumocystis* prophylaxis for leukemic children.[175] Half-strength (200/40 mg) daily TMP-SMX was found to be optimal for *P. jiroveci* prophylaxis in patients with rheumatologic diseases[176]

TMP-SMX has been successfully used with caspofungin to treat severe *P. jiroveci* pneumonia in renal transplant patients.[177] The addition of an echinocandin to TMP-SMX for severe *P. jiroveci* treatment and prophylaxis in heart transplant recipients was associated with decreased mortality in a small, nonrandomized study.[178]

Trimethoprim Use in Pregnancy

The teratogenicity of trimethoprim in humans has not been fully defined, but this drug has not been recommended for use in pregnancy. One study showed an increased risk of neural tube defects, oral clefts, and cardiovascular defects in infants whose mothers received DHFR inhibitors, including trimethoprim, early in pregnancy.[179] However, a subsequent meta-analysis of 24 studies found that TMP-SMX use in HIV-infected pregnant women was generally well tolerated, and in that setting benefits to the mother outweighed potential risks.[101] Trimethoprim is well tolerated in pediatric patients.

ICLAPRIM

Iclaprim is an investigational new diaminopyrimidine, 5-[(2-cyclopropyl-7,8-dimethoxy-2h-chromen-5-yl)methyl]pyrimidine-2,4-diamine. It exists as a racemic mixture of enantiomers with equal inhibitory activity against bacterial DHFRs. The mechanism of action is similar to that of trimethoprim in selectively blocking DHFR and thymidylate biosynthesis, but it has 8- to 32-fold more activity and therefore might be active against trimethoprim-resistant bacteria. Iclaprim showed synergism with sulfonamides but not with other agents against gram-positive or gram-negative organisms.[180]

Iclaprim has in vitro bactericidal activity against many gram-positive cocci including *S. pneumoniae* (MIC_{90} = 0.06–0.25 μg/mL for penicillin-susceptible strains, 2–8 μg/mL for penicillin-intermediate strains, 2–16 μg/mL for penicillin-resistant strains), *S. pyogenes* (MIC_{90} = 0.03–0.06 μg/mL), *Streptococcus agalactiae* (MIC_{90} = 0.25–0.5 μg/mL), *Enterococcus faecalis* (MIC_{90} = 0.06–>32 μg/mL, *Enterococcus faecium* (MIC_{90} = 0.6–0.32 μg/mL), and *S. aureus,* including methicillin-susceptible, methicillin-resistant, vancomycin-intermediate, and trimethoprim-resistant strains. The MIC_{90}s for methicillin-susceptible *S. aureus* (MSSA) range from 0.06 to 0.12 μg/mL, and for MRSA from 0.06 to 0.5 μg/mL.[181] Iclaprim appeared active against two vancomycin-resistant strains of *S. aureus*, but MIC_{90}s against coagulase-negative staphylococci are too high for reliable clinical activity. MIC_{90}s for iclaprim against *N. gonorrhoeae* are 8 μg/mL for penicillin-susceptible and penicillin-resistant strains and 8 μg/mL for ciprofloxacin-resistant strains.[182]

Oral administration results in 40% bioavailability. The IV preparation at a dose of 1.6 mg/kg produces plasma, extracellular lung fluid, and alveolar macrophage levels (0.6 mg/L, 12.6 mg/L, and 24.5 mg/L, respectively) that exceed the MICs for penicillin-susceptible and penicillin-resistant pneumococci for up to 7 and 4 hours, respectively.[183] These levels exceeded the MIC_{90} for MRSA by up to 7 hours. The terminal half-life is about 2 hours, and the drug's hepatic metabolites are excreted in the urine. Although an earlier trial revealed cardiotoxicity, especially QTc prolongation, and did not meet acceptable clinical results, reevaluation at a lower fixed dose of 80 mg infused over 2 hours at 12 hourly intervals has been used in clinical trials. In a phase II study in hospital-acquired pneumonia due to gram-positive pathogens, iclaprim was comparable to vancomycin.[184] In a phase III randomized controlled trial in acute bacterial skin and soft tissue infections caused by gram-positive organisms, compared with vancomycin, IV iclaprim showed noninferiority at an early time point and acceptable safety.[185]

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The complete reference list is available online at Expert Consult.

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35 Quinolones

David C. Hooper and Jacob Strahilevitz

SHORT VIEW SUMMARY

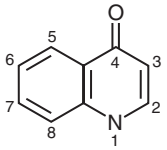
- Usual adult dose
  - Norfloxacin: oral (PO) 400 mg every 12 hours
  - Ciprofloxacin: PO 250 to 750 mg every 12 hours; intravenous (IV) 200 to 400 mg every 12 hours
  - Ofloxacin: PO or IV 200 to 400 mg every 12 hours
  - Levofloxacin: PO or IV 250 to 750 mg daily; 240-mg nebulizer solution (available 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.

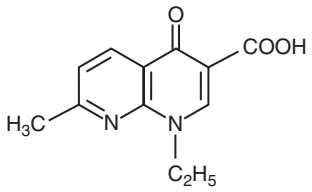
CHEMICAL STRUCTURES

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.

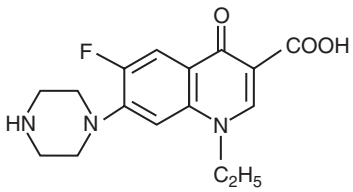
Nalidixic acid is a 1,8-naphthyridine with 1-ethyl and 7-methyl substituents (see Fig. 35.1). Oxolinic acid (quinolone ring; see Fig. 35.1) and cinoxacin (cinnoline ring; not shown in Fig. 35.1) also have 1-ethyl substitutions, as well as a dioxolo ring bridging positions 6 and 7. Potency is greatly 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



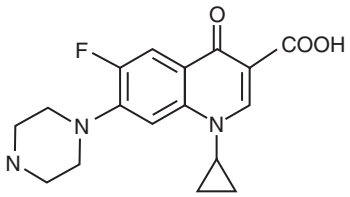
Quinolone Core Structure



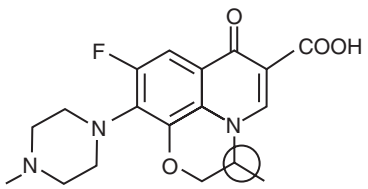
Nalidixic Acid



Norfloxacin

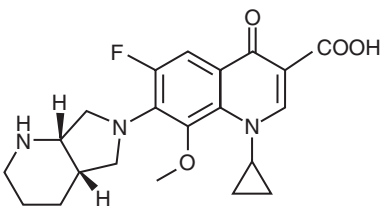


Ciprofloxacin

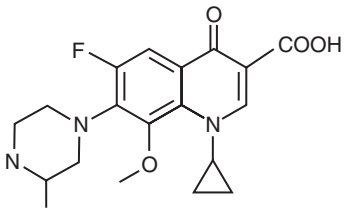


Levofloxacin

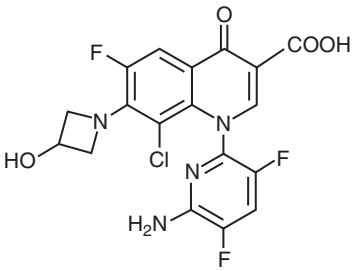
Ofloxacin



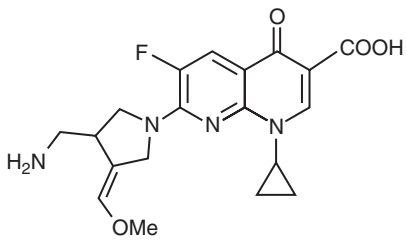
Moxifloxacin



Gatifloxacin



Delafloxacin



Gemifloxacin

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

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

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

(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

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.

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.

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.

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.

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

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]

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,

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

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]

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

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

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

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.*

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

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]