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MINIREVIEW

New Quinolones and Gram-Positive Bacteria

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The quinolone class of antibacterial agents has evolved rapidly to emerge as one of the most effective classes of drugs in the treatment of infectious diseases. While the spectra and antibacterial activities of fluoroquinolones, such as ciprofloxacin, developed in the 1980s improved to include most gram-negative bacteria, their activities against gram-positive bacteria remained limited. However, the 1990s have seen the synthesis and development of several agents such as sparfloxacin and clinafloxacin (PD127391, CI960, and AM-1091) with good activities for gram-positive bacteria (see Table 1). This article reviews the mechanism of action of quinolones for gram-positive bacteria and the mechanisms of resistance by which these organisms evade quinolone action. It focuses on four groups of bacteria: the staphylococci (about which most of the data have been published), the enterococci, the streptococci, and anaerobic gram-positive bacteria.

STAPHYLOCOCCI

Most new fluoroquinolones are at least fourfold more active than ciprofloxacin against staphylococci, including methicillin-resistant strains, regardless of susceptibility to unrelated drugs (Table 1 [ciprofloxacin is shown as the progenitor fluoroquinolone, as it is widely used in the United States and Europe]) (2, 4, 6, 8, 9, 21, 25, 39). All of the new agents described in Table 1 inhibit 90% of staphylococci at concentrations of ≤0.25 μg/ml. For both *Staphylococcus aureus* and coagulase-negative staphylococci, clinafloxacin is the most active agent. It may be anticipated that these new agents will have recommended breakpoint concentrations of 1 to 4 μg/ml; therefore, staphylococci will be well within the therapeutic spectrum of these new agents, although not within that of ciprofloxacin.

All quinolones have a paradoxical lethal effect on bacteria (40); i.e., there is an increase in bactericidal activity with an increase in drug concentration up to an optimum (the optimum bactericidal concentration [OBC]), after which higher concentrations are less bactericidal. The OBC of new fluoroquinolones is usually 10- to 20-fold higher than the MIC of the same agents for both *S. aureus* and *Staphylococcus epidermidis* (Table 2). The biochemical activities of quinolones for DNA gyrase are often determined by measuring the concentration of drug that inhibits either the supercoiling activity of the laboratory-purified enzyme for plasmid DNA or DNA synthesis (Fig. 1) (32, 34). For *Escherichia coli* and other gram-negative bacteria, the concentration of quinolone that inhibits supercoiling of plasmid DNA or DNA synthesis by 50% (IC_{50}) correlates well with the MIC (7, 13, 37). This is also true for staphylococci (Table 2). The correlation between the IC_{50} for DNA synthesis and the quinolone MIC is much better than the correlation between the supercoiling IC_{50} and the same MIC (Fig. 1). This difference between correlations has also been shown for other species, such as *E. coli*. The reason for this discrepancy is either that the DNA gyrase subunits are partially denatured during purification or that supercoiling may not be the best assay for measuring the interaction of quinolones and DNA gyrase. Work by Moreau et al. (26) and Maxwell (23) with *E. coli* suggests that determinations of the inhibition of DNA cleavage by quinolones may be a more appropriate measurement. Biochemical data for *S. aureus* have shown that the targets of quinolones are the A subunits of DNA gyrase encoded by the *gyrA* gene (32, 43).

DNA gyrase is an intracellular enzyme, and so uptake of quinolones into bacteria is important for activity. All quinolones accumulate extremely rapidly within staphylococci and reach a plateau phase (or equilibrium or steady-state concentration) within a few minutes (Fig. 2). Similar data have been obtained for *S. epidermidis* (not shown). No correlation between MICs and steady-state concentrations has been shown for staphylococci (1, 10) as was found for *E. coli* (3, 12). In assays measuring the uptake of up to 100 μg of quinolone per ml, no saturation of accumulation was seen, which suggests that there is no carrier protein involved in transport into staphylococci (24, 38). Accumulation of quinolones in staphylococci is antagonized by cations such as magnesium chloride (34, 38). This phenomenon has already been shown for *E. coli* and quinolones. It was proposed that this antagonism was due to the inhibition of the "self-promoted" uptake pathway by cations (5). This pathway involves an interaction between the drug and the lipopolysaccharide (LPS) of the gram-negative outer membrane (18). However, as gram-positive bacteria do not have an outer membrane or LPS, the antagonism may be due to another mechanism, although gram-positive bacteria do have a molecule similar to LPS, lipoteichoic acid, which may interact in a similar fashion. A simple explanation for the antagonism may be that as quinolones chelate with magnesium (22), the much bulkier chelated quinolone cannot enter the cell. However, this hypothesis requires confirmation.

As with other bacteria, carbonyl cyanide *m*-chlorophenylhydrazone, which dissipates energy, apparently enhances the accumulation of quinolones in staphylococci. In reality, carboxyl cyanide *m*-chlorophenylhydrazone prevents the energy-dependent efflux of quinolones from the cytoplasm (45). Active efflux in *S. aureus* has been shown to be mediated by the NorA protein, which has an amino acid sequence that suggests 12 regions of transmembrane spanning, similar to the energy-dependent efflux pump for tetracycline mediated by the TetA protein (45) and the multidrug efflux transporter of *Bacillus subtilis* (29). Fluoroquinolones are more hydrophilic molecules than agents such as nalidixic acid or chloramphenicol; how-

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TABLE 1. In vitro activities of typical new quinolones for staphylococci, including methicillin-resistant strains[a]

Organism	Agent[b]	MIC (μg/ml)[c]		
		50%	90%	Range
S. aureus	Ciprofloxacin	0.5	1	0.06–8
	Sparfloxacin	0.12	0.25	0.06–0.25
	Temafloxacin	0.12	0.25	0.06–4
	PD 131628	0.06	0.25	0.03–0.5
	DU-6859	0.05	0.1	0.013–0.78
	Tosufloxacin	≤0.03	0.06	≤0.03–0.12
	Clinafloxacin	≤0.008	0.03	≤0.008–0.015
Coagulase-negative staphylococci[d]	Ciprofloxacin	0.12	2	0.12–2
	Temafloxacin	0.25	1	0.12–4
	Sparfloxacin	0.12	0.25	0.06–0.25
	Tosufloxacin	0.06	0.06	≤0.03–2
	DU-6859	0.05	0.39	0.013–0.78
	PD 131628	0.06	0.06	0.03–0.12
	Clinafloxacin	0.015	0.03	≤0.008–0.25

[a] Data are from references 2, 4, 8, 9, and 25.
[b] Agents are shown in descending order of activity.
[c] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[d] Includes *S. epidermidis* and *Staphylococcus saprophyticus*.

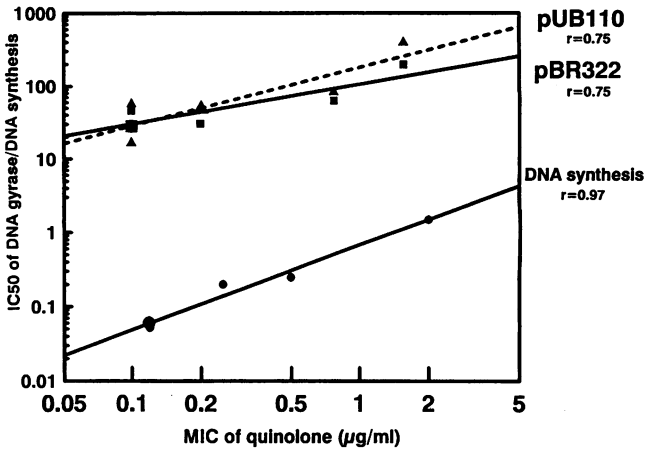

FIG. 1. Inhibition of DNA gyrase or DNA synthesis of *S. aureus* by quinolones. IC_{50}s are given for pUB110 plus purified DNA gyrase (41) (▲), for pBR322 plus purified DNA gyrase (41) (■), and for DNA synthesis of intact cells (33, 36) (●).

ever, there is a range of hydrophilicity, and some agents are more hydrophilic than others. It is thought that the most hydrophilic drugs, e.g., norfloxacin, are effluxed more than less hydrophilic ones such as sparfloxacin. Preliminary data also suggest that the efflux mechanism is depressed during the postantibiotic effect (11). NorA has also been shown to be involved in resistance to some fluoroquinolones, with 16- to 64-fold decreases in susceptibility to ciprofloxacin, norfloxacin, enoxacin, and ofloxacin. This has also been related to the degree of hydrophilicity of the drug, as there is only a two- to fourfold rise in the MICs of nalidixic acid, oxolinic acid, and sparfloxacin for the resistant strain. It has been shown that the DNA sequences of the $NorA^r$ and $NorA^s$ genes differ by just one base pair, so that alanine is substituted for aspartate at the 27th residue from the carboxy terminus of the protein (33). However, Kaatz and Seo (20) suggest that this mutation is not responsible for quinolone resistance and that resistance is due to a mutation in the regulator locus. The epidemiology of resistance due to the $NorA^r$ gene has not been well reported, although one clinical isolate was described as having *norA* located on a plasmid (42); however, it was not determined whether this was a mutated *norA* gene, a gene duplication, or a regulatory mutation.

Trucksis et al. (44) have shown by digesting the chromosomal DNA of *S. aureus* with the restriction enzyme *Sma*I that there are three loci associated with quinolone resistance. Fragment A is associated with resistance to quinolones and novobiocin, fragment D is associated with *norA*, and fragment G is associated with mutations in *gyrA*. GyrA-mediated resistance is probably the most important mechanism of quinolone

TABLE 2. Interaction of quinolones and NCTC type strains and mutants of gram-positive bacteria[a]

Species and strain	MIC (μg/ml)			CIP		TOS		SPAR		DNA IC_{50} (μg/ml)			SSC[b] (μg/ml)		
	CIP	TOS	SPAR	OBC (μg/ml)	Log drop[c]	OBC (μg/ml)	Log drop	OBC (μg/ml)	Log drop	CIP	TOS	SPAR	CIP	TOS	SPAR
S. aureus															
NCTC 8532 (F77)	0.5	0.12	0.06	4.5	4	2.5	5	3	3	0.2	0.25	0.03	41.4	70	150
F77C2	4	—[d]	0.25	—	—	—	—	—	—	0.9	—	0.85	51	—	—
S. epidermidis															
NCTC 11047 (F78)	0.25	0.06	0.12	2.5	1	0.9	3	2	1	0.11	0.03	0.11	86	34	180
F78T7	8	32	2	—	—	—	—	—	—	—	4.8	—	—	20	—
E. faecalis															
NCTC 775 (M1)	1	1	1	4	1	5	1	5	1	1.5	1.84	1.2	28	41	—
M1C2	8	8	8	—	—	—	—	—	—	1.59	—	—	18		—
E. faecium NCTC 7171 (M2)	8	8	2	30	1	150	1	10	1	6.6	18.3	3.4		38	—
S. pneumoniae															
NCTC 7465 (M4)	1	0.25	0.5	10	1	8	1.6	9	1.4	2.4	0.36	0.6	24	3.4	—
M4C1	16	1.25	1.25	—	—	—	—	—	—	25.6	7.32	1.63	29	3.5	—

[a] CIP, ciprofloxacin; TOS, tosufloxacin; SPAR, sparfloxacin.
[b] SSC, steady-state concentration.
[c] Log drop is the number of logarithmic decreases in the viable count at the OBC after a 1-h exposure to quinolone.
[d] —, not determined.

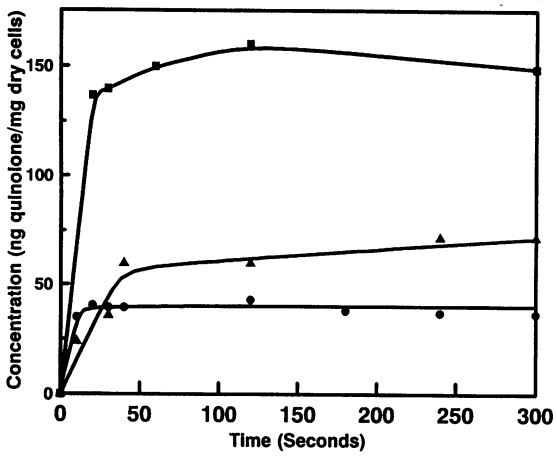

FIG. 2. Accumulation of quinolones in *S. aureus*. Symbols: ■, 10 μg of sparfloxacin per ml; ▲, 20 μg of tosufloxacin per ml (this agent fluoresces poorly); ●, 10 μg of temafloxacin per ml.

resistance in staphylococci in the clinical setting in the United States and Europe (Table 3). Essentially, most mutations occur at serine 84, which is analogous to serine 83 in GyrA of *E. coli*, although other mutations in *S. aureus* at amino acid positions 85 and 88 have also been detected (41). High-level resistance has been shown to occur in *S. aureus* when mutations occur at both positions 84 and 85 (16, 41). It is very worrying that there are multiple mutations within one gene giving rise to high-level resistance (>128 μg of ciprofloxacin per ml), because while the isolates with only one mutation in *gyrA* would have decreased susceptibility to some of the newer quinolones such as clinafloxacin, organisms with multiple mutations would be resistant to even the agents under development (Table 4). In addition, if *norA* is plasmid encoded, there is the possibility of not only multiple mutations in *gyrA* but also multiple mechanisms of resistance within one strain; this could also lead to problems for new quinolones.

For ciprofloxacin and sparfloxacin, frequencies of mutation to resistance obtained in the laboratory range from $\sim 10^{-6}$ to $\sim 10^{-11}$ depending on the agent and the selecting concentration (38); these frequencies suggest a mutation at a single locus. For some of the newer agents such as tosufloxacin or temafloxacin, it was difficult to select resistant bacteria at concentrations of ≥2 μg of quinolone per ml. The frequencies of resistance for oxacillin- or methicillin-resistant staphylococci are similar to those for wild-type susceptible strains (15). Despite an association between methicillin resistance and quinolone resistance suggested in the literature, in well-characterized isolates, no cross-resistance by a single mechanism has been seen and quinolones do not affect penicillin-binding protein expression. The numbers of resistant staphylococci vary widely and depend on geography (country or institution), the use of the drug, and infection control. Widespread indiscriminate use of quinolones, such as ciprofloxacin, has led to high frequencies of resistance in some institutions. In addition, transfer of one or two quinolone-resistant strains within one institution can also lead to apparently high levels of resistance. Therefore, great care must be taken in the use of these agents. For postciprofloxacin therapy or laboratory-selected quinolone-resistant strains, the MICs of ciprofloxacin are above the recommended breakpoint concentration for many countries. Although the MICs of the newer agents such as sparfloxacin and clinafloxacin are increased (15) (Table 4), not all ciprofloxacin-resistant strains would be clinically resistant to the new agents.

STREPTOCOCCI

Streptococci are less susceptible than staphylococci to the newer fluoroquinolones, but 90% of the strains examined so far would be inhibited by 1 μg of the fluoroquinolones listed in Table 5 per ml (4, 9, 21, 25, 31). As with the staphylococci, clinafloxacin is the most active agent so far. If the recommended breakpoint concentrations of new quinolones are 1 to 4 μg/ml (Table 5), most streptococci would be within the therapeutic spectra of these new agents. No DNA gyrase data have been published for streptococci, but DNA synthesis IC_{50}s for pneumococci correlate well with the MICs (Table 2) (36). As with other bacteria, all quinolones have a paradoxical effect: at 5- to 20-fold-greater concentrations than the MIC, optimum killing is seen. After 1 h of exposure at the OBC, there was at least one logarithmic drop in the viable count. The kinetics of accumulation of quinolones in pneumococci and other streptococci is similar to that for other bacteria: accumulation is very rapid, so that within a couple of minutes, a steady-state concentration is obtained (Fig. 3). Lower concentrations of

TABLE 3. Resistance in staphylococci due to mutations in *gyrA*

Species	CIP MIC[a] (μg/ml)	Position(s)	Codon	Amino acid change	No. (%) of strains with mutation (n = 28)[b]
S. aureus	0.5	84	TCA		
S. aureus	16–128	84	TTA	Serine to leucine	16 (57)
S. aureus	16	84	GCA	Serine to alanine	3 (11)
S. aureus	0.5	85	TCT		
S. aureus	64	85	CCT	Serine to proline	
S. aureus	>256	84, 85	TTA, CCT	Serine to leucine and serine to proline	3 (11)
S. aureus	0.5	88	GAA		
S. aureus	16–32	88	AAA	Glutamine to lysine	6 (21)
S. epidermidis[c]	0.25	84	TCT		
	16	84	TTT	Serine to phenylalanine	

[a] CIP, ciprofloxacin.
[b] Data from reference 16.
[c] Data from reference 41.

TABLE 4. In vitro activities of quinolones for ciprofloxacin-resistant staphylococci

Organism	MIC (μg/ml)[a]:						
	CIP		SPAR	TOS	CLIN	PD131	WIN
	Pretherapy	Posttherapy					
S. aureus[b]	0.5	4					
S. epidermidis[c]	0.25	16					
S. aureus[d]	0.5	4	0.25–2	0.5–8			
S. epidermidis[d]	0.25	8	2–4	8			
S. aureus norA[d]		16	0.25	1	0.25		
S. aureus sa35 (Ser-85→Pro)[d]		64	2	8	1		
S. aureus sa146 (Ser-85→Pro, Ser-84→Leu)[d]		128	16	4	1		
Cip[r] *S. aureus*[e]		8–128	2–16		0.25–8	4–128	0.06–1
Cip[r] coagulase-negative strains[e]		4–128	2–16		0.12–1	1–8	0.25–4

[a] CIP, ciprofloxacin; SPAR, sparfloxacin; TOS, tosufloxacin; CLIN, clinafloxacin; PD131, PD117 596-2; WIN, win52723.
[b] Data from reference 19.
[c] Data from reference 41.
[d] Data from reference 33a.
[e] Data from reference 15.

quinolones are accumulated by pneumococci than by staphylococci (Table 2).

An in vitro study of the selection of quinolone-resistant pneumococci showed that the frequency of mutation to resistance is of the order associated with a mutation at a single locus (35). The increases in the MICs of quinolones, without cross-resistance to unrelated agents, suggest that the mutants probably contain mutations in the gene(s) encoding DNA gyrase. The DNA synthesis IC_{50}s also showed corresponding increases correlating with the MICs for the resistant strains (36). Accumulation of quinolones in the mutants was similar to that in the parent wild-type strain. Unlike that in staphylococci, the epidemiology of quinolone resistance in streptococci has not been well documented, and while in some institutions up to 40% of staphylococci have been reported to be resistant to ciprofloxacin (17), this is not the case for pneumococci or other streptococci. In Madrid, where penicillin-resistant pneumococci are prevalent, in 1990 only 3% were resistant to ciprofloxacin, and in 1991 no resistance to ciprofloxacin was seen (22a). It may be that as these streptococci are inherently less susceptible to the currently available quinolones, they are less likely to have been exposed to these agents; therefore, the potential for resistance remains to be determined.

TABLE 5. In vitro activities of quinolones for streptococci[a]

Organism	Agent	MIC (μg/ml)[b]		
		50%	90%	Range
S. pneumoniae[c]	Ciprofloxacin	0.5	1	0.06–4
	Temafloxacin	0.5	1	0.25–1
	Sparfloxacin	0.25	0.25	0.12–0.5
	Tosufloxacin	0.12	0.25	0.06–0.5
	PD 131628	0.12	0.25	0.03–0.5
	DU-6859	0.1	0.1	0.025–0.1
	Clinafloxacin	0.03	0.06	≤0.008–0.06
Group A streptococci[d]	Ciprofloxacin	0.5	0.5	0.25–0.5
	Sparfloxacin	0.25	0.5	0.25–0.5
	Temafloxacin	0.25	0.5	0.25–4
	Tosufloxacin	0.25	0.25	0.06–>16
	DU-6859	0.1	0.1	0.025–0.2
	PD 131628	0.12	0.12	0.06–0.12
	Clinafloxacin		0.06	≤0.008–0.06
Group B streptococci[e]	Ciprofloxacin	0.5	1	0.12–1
	Temafloxacin	0.5	1	0.06–1
	Sparfloxacin	0.5	0.5	0.25–0.5
	PD 131628	0.25	0.5	0.25–0.5
	Tosufloxacin	0.25	0.25	0.12–0.25
	Clinafloxacin	0.12	0.12	0.015–0.06
Streptococcus viridans	Ciprofloxacin	1	4	0.12–8
	Temafloxacin	0.06	0.12	0.008–1
	Clinafloxacin	0.03	0.06	≤0.007–0.06

[a] Data are from references 4, 9, 21, 25, and 31.
[b] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[c] Includes penicillin-resistant strains.
[d] Includes *Streptococcus pyogenes*.
[e] *Streptococcus agalactiae*.

ENTEROCOCCI

Enterococcus faecium tends to be more resistant to antimicrobial agents than *Enterococcus faecalis*, and this trend is also seen for the quinolones listed in Table 6 (2, 4, 8, 9, 25). The new quinolones are less active against the enterococci than

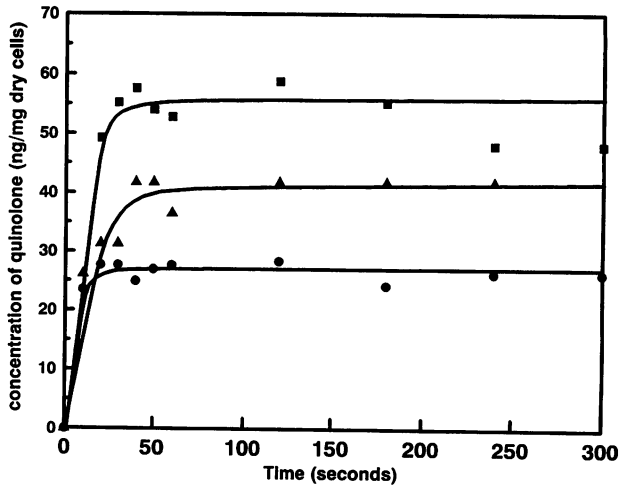

FIG. 3. Accumulation of quinolones in enterococci and *Streptococcus pneumoniae*. Symbols: ■, 10 μg of ciprofloxacin per ml and *S. pneumoniae*; ▲, 20 μg of tosufloxacin per ml and *E. faecalis*; ●, 10 μg of ciprofloxacin per ml and *E. faecalis*.

TABLE 6. In vitro activities of quinolones for enterococci[a]

Species	Agent	MIC (μg/ml)[b]		
		50%	90%	Range
E. faecium	Ciprofloxacin	2	4	0.5–4
	Sparfloxacin	1	1	0.5–1
	Tosufloxacin	1.56	25	0.2–25
	Temafloxacin[c]	1	4	0.25–16
	DU-6859	0.39	1.56	0.05–6.25
	Clinafloxacin	0.12	0.5	0.015–0.5
E. faecalis	Ciprofloxacin	1	4	0.25–4
	Temafloxacin	1	4	0.5–4
	Tosufloxacin	0.78	3.13	0.2–12.5
	Sparfloxacin	0.5	1	0.5–1
	DU-6859	0.2	0.39	0.1–1.56
	Clinafloxacin	0.25	0.25	0.01–1

[a] Data are from references 2, 4, 8, 9, 25, and 31.
[b] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[c] This agent was tested against *E. faecium*, *E. faecalis*, *Enterococcus durans*, and *Enterococcus hirae*.

against the streptococci and staphylococci; therefore, not all the new agents would be active if the recommended breakpoint concentrations were 1 to 4 μg/ml. As observed from the in vitro data, only clinafloxacin inhibited 90% of *E. faecium* and *E. faecalis* at a concentration of ≤1 μg/ml. The OBCs for the bactericidal activities of the new agents are 4- to 10-fold greater than the MICs of the same agents (Table 2). However, at the OBC, there was no more than one logarithmic decrease in the viable count, suggesting that quinolones are bacteriostatic against enterococci. Accumulation of quinolones in enterococci is rapid, with accumulated concentrations similar to those in pneumococci (Table 2 and Fig. 3; also unpublished data). Similar data have been obtained by Nakanishi et al. (28). The DNA synthesis IC_{50}s compared well with the MICs (Table 2).

Quinolone-resistant enterococci have been selected in the laboratory at frequencies of 10^{-7} to 10^{-9} at 2 μg of sparfloxacin or ciprofloxacin per ml, which suggests a mutation at a single locus (unpublished data). However, for newer drugs such as tosufloxacin, triplicate experiments did not select any resistant mutants, so perhaps as in the case of the staphylococci, some of the newer drugs are less able to select quinolone-resistant mutants. For quinolone-resistant bacteria, as with other bacteria, when there is an increase in the MIC, there is an increase in the IC_{50} for DNA synthesis. The IC_{50}s for purified enterococcal DNA gyrase-mediated supercoiling of plasmid DNA (pBR322) were much higher than the MICs but were also increased for resistant strains compared with the values for sensitive strains (28). While for many resistant mutants the IC_{50} for DNA synthesis correlates well with the MIC, suggesting a mutation in *gyrA* causing resistance, for some strains it did not increase to the MIC. These mutants also had decreased accumulation (33a).

ANAEROBIC GRAM-POSITIVE BACTERIA

For anaerobic gram-positive bacteria, only MIC data have been published so far for the agents listed in Table 7 (2, 4, 8, 9, 14, 25, 31). Unlike the case with aerobic gram-positive bacteria, not all newer quinolones are active against anaerobes. There are also variations in susceptibility between species of the same genus: *Clostridium difficile* is less susceptible to quinolones than *Clostridium perfringens*. It has been proposed by some workers that quinolones require oxygen to be bactericidal (27); however, the data for new agents with low MICs

TABLE 7. In vitro activities of quinolones for anaerobic gram-positive bacteria[a]

Species	Agent	MIC (μg/ml)[b]		
		50%	90%	Range
Peptostreptococci	Ciprofloxacin	1	2	0.25–4
	Sparfloxacin	1	4	0.25–4
	Temafloxacin	0.5	1	0.12–8
	Tosufloxacin	0.39	0.79	0.39–0.78
	DU-6859	0.1	0.2	0.1–0.39
	Clinafloxacin	0.03	0.5	0.015–0.5
C. perfringens	Ciprofloxacin	1	1	0.25–2
	Sparfloxacin	0.25	0.5	1–2
	Temafloxacin	0.5	1	0.12–1
	PD 131628[c]	0.25	0.5	0.06–2
	Clinafloxacin	0.06	0.12	0.06–0.12
C. difficile	Ciprofloxacin	8	16	1–32
	Temafloxacin	4	8	1–8
	Sparfloxacin[c]	2	8	0.25–16
	Clinafloxacin[c]	0.25	0.5	0.03–1

[a] Data are from references 2, 4, 8, 9, 14, 21, and 25.
[b] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[c] This agent was tested against multiple *Clostridium* spp.

suggest that this is unlikely. It is possible that anaerobic organisms are inherently less susceptible to quinolones because of a less susceptible DNA gyrase or that the pH of the environment in which these organisms grow affects the pK_a of quinolones, making them less active. DNA gyrase is a ubiquitous enzyme among the bacterial species examined so far and has been isolated from the gram-negative anaerobe *Bacteroides fragilis*. Therefore, it may be assumed that this enzyme also exists in gram-positive anaerobes and is the target for quinolone action.

CLINICAL CHALLENGE FOR NEW QUINOLONES OF INFECTIONS BY GRAM-POSITIVE BACTERIA

Quinolones, such as ciprofloxacin, have been widely used for the treatment of staphylococcal infections, but because of the emergence and dissemination of resistant strains and the multiple mechanisms of resistance that staphylococci can elaborate, it is necessary to exercise caution in quinolone use. New quinolones with markedly improved activities compared with that of ciprofloxacin are required for the treatment of staphylococcal infections, as the MICs of ciprofloxacin for many staphylococci are close to the recommended breakpoint concentration. It remains to be seen whether the quinolone-resistant strains that have arisen so far will be clinically susceptible to the newer agents. For streptococci, although agents such as ciprofloxacin are concentrated in the mucosa and high levels can be achieved at the site of infection compared with levels in serum, the newer agents are so much more active against organisms such as pneumococci that clinicians may well have greater confidence in the use of quinolones in the treatment of respiratory tract infections. Moreover, resistant streptococci are rare at the moment. Because such high levels of currently available quinolones are achieved in the bladder and prostrate, it is not clear whether new quinolones are required for the treatment of enterococcal infections which predominantly occur at these sites. In addition, there is confusion as to the role for quinolones against anaerobic bacteria, since agents that are active against anaerobes may disturb the fecal flora and cause gastrointestinal

disturbances. However, it was suggested that newer quinolones do not disturb the fecal flora because of binding to fecal matter (30), and so there may well be a role for these agents in the treatment and/or prophylaxis of anaerobic infections.

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