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Activity of Newer Fluoroquinolones *In Vitro* Against Gram-Positive Bacteria

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Abstract

Several newer fluoroquinolones, which have been recently introduced or are under investigation, display substantially greater potency against Gram-positive organisms than the older generation agents of this class. Nevertheless, for problem organisms including methicillin-resistant strains of *Staphylococcus aureus* and many *Enterococcus faecium*, concentrations of newer antimicrobials required to inhibit 90% of organisms in the collections studied remain above those that are projected to be achievable with clinical use. Nevertheless, enhanced potency of several newer quinolones may result in a favourable pharmacodynamic profile leading to improved outcomes against Gram-positive infections and possibly to the delayed or diminished emergence of resistance to these agents.

A major recent focus in antimicrobial chemotherapy has been the development of fluoroquinolones with enhanced activity against Gram-positive bacteria. The usefulness of early fluoroquinolones against common pathogens, including *Staphylococcus aureus* and enterococci, has been limited by the significant prevalence of resistance to these agents among current isolates.[1] It is also hoped that the development of agents with increased potency against *Streptococcus pneumoniae* will extend the usefulness of these agents in the treatment of pneumococcal infections and prolong the life of the antimicrobial class by reducing the likelihood that resistance will emerge among clinical isolates. This paper will review the *in vitro* activities of several newer agents against Gram-positive organisms, with the exception of *S. pneumoniae*, which will be covered in another paper in this series. Data will be drawn from published sources pertaining to a variety of agents tested against recent collections of organisms to explore the potential utility of this class. This review will include discussion of agents that may not be developed further for clinical use but which may serve to illustrate the spectrum of this class. Several of the compounds that will be discussed were included in a previous review of this topic.[2] The present manuscript will complement and extend information provided earlier.

1. Staphylococci

1.1 *Staphylococcus aureus*

The *in vitro* activities of several agents against methicillin-susceptible and methicillin-resistant strains of *S. aureus* are shown in table I. Shown for comparison is the range of MIC_{90} values of ciprofloxacin, which illustrates the fact that many of the methicillin-resistant strains are resistant to ciprofloxacin and older members of the fluoroquinolone class. Among the most potent agents are sitafloxacin, LB 20304 (SB-265805), and nadifloxacin which is a fluoroquinolone investigated for topical use.[29] The agents designated NSFQ-104 and NSFQ-105 are sulphonyl analogues of norfloxacin and ciprofloxacin, respectively.[32] From the table I it is evident that the sulphonyl analogue is more active than ciprofloxacin. It is believed that the sulphonyl group contributes to enhanced permeability, but there is no evidence that any sulphonamide-like activity contributes to the potency of the compounds.[33] Against susceptible isolates of *S. aureus*, the newer fluoroquinolones are generally bactericidal at concentrations close to the minimum inhibitory concentrations (MIC).[3,19,24] In 19 of 24 studies reviewed for this manuscript, the MIC_{50} of ciprofloxacin against methicillin-resistant *S. aureus* exceeded 2 mg/L.

Table I. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against *Staphylococcus aureus*. MIC_{90} values of ciprofloxacin are shown in parentheses where available

Agent	MIC_{90} (mg/L) against		
	MSSA	MRSA	Reference
Levofloxacin	0.25-0.5 (0.25-1)	8-≥16 (>4->100)	3-8
Sparfloxacin	0.06-0.25 (0.5-3.13)	8-25 (>4->100)	4,5,7,9
Grepafloxacin	0.12 (0.78-1)	>4 (>2-50)	10,11
Trovafloxacin	0.015-0.12 (0.5-2)	1-8 (>4->100)	5,6,8,9,11-17
Moxifloxacin	0.06-0.12 (0.5-1)	2-4 (32-128)	3,6,11,18
Gatifloxacin	0.1-0.25 (0.5-2)	6.25-16 (32-100)	6,12,19
Clinafloxacin	0.03-0.12 (0.5-2)	1-8 (32->128)	6,20-22
Sitafloxacin	0.03-0.25 (0.5-1)	0.78-3.13 (>4-≥100)	8,23-26
Balofloxacin	0.2 (3.13)	6.25 (50)	9
LB 20304	0.03-0.06 (0.5-2)	1-2 (>4-32)	7,27
Nadifloxacin	0.06-0.1 (0.25-3.13)	1.56 (>100)	28,29
Pazufloxacin	0.39 (0.39-0.78)	12.5-100 (≥100)	17,30
Rufloxacin	2-64 (≤16)		31
NSFQ104	0.25 (0.5)	>128 (>64)	32
NSF2105	0.03 (0.5)	4 (>64)	32

MRSA = methicillin-resistant *S. aureus*; **MSSA** = methicillin-susceptible *S. aureus*.

Table II. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against coagulase-negative staphylococci. MIC_{90} values of ciprofloxacin are shown in parentheses

Agent	MIC_{90} (mg/L) against		
	MSS	MRS	Reference
Levofloxacin	0.25-1 (0.25-0.5)	2-8 (4-32)	4,7,8
Sparfloxacin	0.5 (0.25-1.56)	3.1-8 (4-32)	4,7,8,9,13,23,24,27
Grepafloxacin	0.12 (0.39-0.5)	>4 (>2)	10,34
Trovafloxacin	0.03-4 (0.25-8)	0.5-4 (4-64)	7,8,11,13-15
Moxifloxacin	0.12-2 (0.5-8)	2 (≥32)	11,18
Clinafloxacin	0.03-0.06 (0.25-0.5)	0.5-1 (32-128)	20-22
Sitafloxacin	0.015-0.1 (0.25-0.78)	0.12-0.39 (>4-25)	8,23-26
Balofloxacin	0.2 (1.56)		9
LB 20304	0.015-0.13 (0.25-1)	0.25-1 (4-32)	7,27
Nadifloxacin	4 (>8)		29
Pazufloxacin	0.2-0.39 (0.39)	0.2-6.25 (0.2-6.25)	17,30

MRS = methicillin-resistant strains; **MSS** = methicillin-susceptible strains.

1.2 Coagulase-Negative Staphylococci

Activities of several newer quinolones against methicillin-susceptible and methicillin-resistant strains of coagulase-negative staphylococci are shown in table II. As was the case for *S. aureus*, fluoroquinolone resistance is more prevalent among the methicillin-resistant strains. Nevertheless, a number of the newer agents retain substantial potency, as demonstrated against collections of resistant organisms. For example, trovafloxacin,[7,8,11,13-15] clinafloxacin,[20-22] sitafloxacin,[8,23-26] LB 20304[7,27] and moxifloxacin,[11,18] inhibited a substantial proportion of strains at concentrations ≤1mg/L. The high levels of activity of newer fluoroquinolones have also been documented for species other than *S. epidermidis*.[6,10,12,14,18] In the study by Bauernfeind,[6] clinafloxacin, moxifloxacin and gatifloxacin were active against methicillin-susceptible and -resistant strains of *S. haemolyticus* as well as *S. epidermidis*. Methicillin-resistant strains of *S. saprophyticus* were more resistant to the 3 new compounds (MIC_{90} values of 0.5, 1, 8 mg/L, respectively). *S. hominis, S. cohnii, S. simulans*, and others, were all inhibited by low concentrations of these agents.

2. Streptococci

As mentioned above, the activities of the fluoroquinolones against *S. pneumoniae* will be discussed separately.

2.1 *Streptococcus pyogenes*

Table III illustrates that the activities of several newer fluoroquinolones against group A streptococci are substantially higher than those of older members of this class. For example, in 1 study,[14] the MIC_{90} values of ciprofloxacin and ofloxacin were 16 mg/L, while the MIC_{90} of trovafloxacin against this collection was 0.25 mg/L. Trovafloxacin was the most active of the compounds currently approved for use in the US, but several of the newer compounds under development demonstrate equal or greater potency. There

does not appear to be a consistent method-dependent trend in activities determined in these studies.

2.2 *Streptococcus agalactiae*

As shown in table IV, the newer fluoroquinolones demonstrate greater potency against group B streptococci than do older members of this class. With the exception of pazufloxacin, all of the newer agents shown in table IV inhibit 90% of the organisms studied at concentrations of 0.5 mg/L or less.

2.3 Other Streptococci

Table V provides information concerning the activities of fluoroquinolones against *viridans* group streptococci and strains classified as *S. milleri*. Both groups of organisms appear to be quite susceptible to trovafloxacin, moxifloxacin, clinafloxacin and sitafloxacin.

3. Enterococci

3.1 *Enterococcus faecalis*

A number of the newer agents have demonstrated improved activity against ciprofloxacin-susceptible strains of *E. faecalis* (table VI). However, it is evident from table VI that reduced susceptibility to the newer agents parallels increases in the MIC values of ciprofloxacin. Sitafloxacin[8,23,24,26] and clinafloxacin[6,20,21,37] display the greatest activity against strains showing substantial resistance to ciprofloxacin (MIC values ≥32 mg/L), with MIC_{90} values of the new compounds as low as 1 mg/L. Several collections from which these data are drawn include vancomycin-resistant strains of *E. faecalis*.

Table III. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against *Streptococcus pyogenes*

Agent	MIC_{90} (mg/L)	Reference
Ciprofloxacin	0.25-4[a]	3-7,9,11-14,16-26,30,34-36
Ofloxacin	1-4[a]	3-5,7,9,14,17-19,23-25,27,30, 34,35
Levofloxacin	0.5-1	3-7
Sparfloxacin	0.38-3.13	4,5,7,9,12,13,19,23,24,27,35
Grepafloxacin	0.39	34
Trovafloxacin	0.06-0.25	5-7,11-14,16
Moxifloxacin	0.12-0.25	3,6,11,18
Gatifloxacin	0.39-0.5	6,12,19
Clinafloxacin	0.06-0.5	6,20-22
Sitafloxacin	0.03-0.1	23-26
Balofloxacin	0.39	9
LB 20304	0.015-0.03	7,27
CFC 222	1.0	35
MF 961	2	31
Pazufloxacin	3.13	17,30
Rufloxacin	16-32	31,36

a In reference,[5] MIC_{90} of ciprofloxacin, ofloxacin was 16 mg/L; MIC_{90} of trovafloxacin was 0.25 mg/L.

Table IV. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against *Streptococcus agalactiae*

Agent	MIC_{90} (mg/L)	Reference
Ciprofloxacin	0.5-4	4-7,11-14,16,18,20-22,25, 26,30,31
Ofloxacin	1-2	4,5,7,14,18,25,30
Levofloxacin	0.5-1	4-7
Sparfloxacin	0.25-1	4,5,7,12
Trovafloxacin	0.12-0.5[a]	5-7,11-14,16
Gatifloxacin	0.5	6,12
Moxifloxacin	0.25-0.5	6,11,18
Clinafloxacin	0.12-0.25	6,20-22
Sitafloxacin	0.06	25,26
LB 20304	0.03	7
Pazufloxacin	3.13	30

a In reference,[5] MIC_{90} of trovafloxacin was 8 mg/L.

Table V. Representative minimum inhibitory concentrations (MIC_{90} values) of fluoroquinolones against other streptococci

Agent	MIC_{90} (mg/L) against	
	Viridans group	*S. milleri*
Ciprofloxacin	1-8	1-2
Levofloxacin	1-2	1-2
Sparfloxacin	0.25-1	0.5
Trovafloxacin	0.12-0.25	0.12-0.25
Moxifloxacin	0.25-0.5	0.06-0.25
Clinafloxacin	0.06-0.25	0.25
Sitafloxacin	0.12	0.06
Reference	3-5,14,15,18,20-22	6,8,11,12

3.2 *Enterococcus faecium*

The potential to develop quinolone-like drugs with enhanced potency against enterococci is illustrated by the 2-pyridone compound, designated A-86719.1 (ABT-719). This class of agents, while technically not fluoroquinolones, does bear a structural resemblance to fluoroquinolones.[21,22] Although this specific agent is not a candidate for further development, it inhibited 90% of *E. faecium* and *E. faecalis* at concentrations of 0.5 to 1 mg/L.[21,22]

A striking feature of the data shown in table VII is the paucity of information concerning fluoroquinolone-susceptible *E. faecium*, as these organisms are becoming increasingly hard to find. Table VII illustrates that most ciprofloxacin-resistant strains of this species would be expected to be resistant to newer agents as well, even though the newer agents do have increased intrinsic potency. Sitafloxacin[8,23,24,26] was the most active agent against these organisms.

3.3 Other Enterococcal Species

Few reports provide data on specific enterococcal species other than *E. faecium* and *E. faecalis*. For *E. casseliflavis*, the MIC_{90} values of levofloxacin, sparfloxacin and clinafloxacin were 4, 1, and 0.5 mg/L, respectively.[4,21] Some strains of *E. gallinarum* appear

Table VI. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against *Enterococcus faecalis* collections, grouped on the basis of reported ciprofloxacin MIC_{90} values

Agent	MIC_{90} (mg/L) when ciprofloxacin MIC_{90} is			
	<4	4-16	≥32	Reference
Ofloxacin	2-6.25	8	≥32	4,5,9,14,15,17-19,23,24,30,34,35
Levofloxacin	2		≥32	4-6,8,37
Sparfloxacin	0.39-3.13	1.0	≥16	4,5,8,9,13,19,23,24,27,35,37
Grepafloxacin	0.39	>4		10,34
Trovafloxacin	0.25-2	2	16	5,6,8,11,13-15,37
Gatifloxacin	0.78	2		6,19
Moxifloxacin	0.5	1.0	8	6,11,18
Clinafloxacin	0.25	1.0	1-4	6,20,21,37
Sitafloxacin	0.2-0.39		1.0	8,23,24,26
Balofloxacin	0.78			9
LB 20304			4	27
CFC 222		1.0		35

Table VII. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against *Enterococcus faecium* collections, grouped on the basis of ciprofloxacin MIC_{90} values

Agent	MIC_{90} (mg/L) of agent when ciprofloxacin MIC_{90} is			
	<4	4-16	>16	Reference
Ofloxacin	3.13	8-32	≥32	4,5,9,17-19,23,24,34,37
Levofloxacin		4-8	≥32	4-6,8,37
Sparfloxacin	0.78	1-2	≥16	4,5,8,13,19,23,24,37
Trovafloxacin		2-8	≥12.5	5,6,8,11,13,14,37
Gatifloxacin		4	12.5	6,19
Moxifloxacin		2-4	16	6,11,18
Clinafloxacin	0.25	1-4	≥8	6,20-22,37
Sitafloxacin			0.78-2	8,23,24,26
Balofloxacin	1.56			9

to be more resistant to the fluoroquinolones, with MIC_{90} values of 2 mg/L for clinafloxacin, trovafloxacin and moxifloxacin, and 4 mg/L for gatifloxacin.[6] There does not appear to be a significant difference in susceptibility to fluoroquinolones between *E. avium* and *E. raffinosus* based on a comparison of MIC_{90} values.[4,13,21]

4. Other Gram-Positive Organisms

4.1 *Listeria monocytogenes*

The older generation of fluoroquinolones including ciprofloxacin, ofloxacin and levofloxacin inhibited 90% of *L. monocytogenes* strains at concentrations between 1 and 4 mg/L. Trovafloxacin is approximately 10-fold more active, with MIC_{90} values between 0.25 and 0.5 mg/L (table VIII). The investigational agents gatifloxacin, moxifloxacin and clinafloxacin do not appear to be obviously superior to trovafloxacin in this regard, although extensive data do not exist.

4.2 Uncommon Pathogens

Reported MIC_{90} values of the older fluoroquinolones against *Corynebacterium jeikeium* vary widely: for example, reported MIC_{90}s for ciprofloxacin range between 1 and ≥64 mg/L.[4,5,7,13,15,21] The newer agents are generally more potent, but inhibitory concentrations remain relatively high. For example, collections with MIC_{90} values of ciprofloxacin >4 mg/L, yielded MIC_{90}s of sparfloxacin and trovafloxacin ≥8 mg/L,[13,15] LB 20304 = 4 mg/L,[7] and clinafloxacin = 2 mg/L.[21]

Against *Lactobacillus* spp., we have reported MIC_{90} values of ciprofloxacin or ofloxacin between 2 and 8 mg/L.[4,13,21] In these studies, the MIC_{90}s of sparfloxacin were 0.25 to 2 mg/L. The MIC_{90} of clinafloxacin was 0.12 for a collection with a ciprofloxacin MIC_{90} of 2 mg/L, and the MIC_{90} of trovafloxacin was 2 mg/L when the ciprofloxacin MIC_{90} was 8 mg/L.

Table VIII. Representative minimum inhibitory concentrations (MIC_{90}) of fluoroquinolones against *Listeria monocytogenes*

Agent	MIC_{90} (mg/L)	Reference
Ciprofloxacin	1-2	4-6,13,15,21,22
Ofloxacin	2-4	4,5,15
Levofloxacin	1-2	4-6
Sparfloxacin	2-4	4,5,13
Trovafloxacin	0.25-0.5	5,6,13,15
Gatifloxacin	0.5	6
Moxifloxacin	0.5	6
Clinafloxacin	0.12-0.5	6,21,22

Few isolates of the intrinsically vancomycin-resistant *Leuconostoc* spp. and *Pediococcus* spp. have been studied. For *Leuconostoc*, we have reported ciprofloxacin, sparfloxacin, trovafloxacin and clinafloxacin MIC_{90} values of 4, 2, 0.5 and 0.25 mg/L, respectively.[4,13,21] Pediococci in our collection were more resistant to ciprofloxacin (MIC values 16 to 32 mg/L).[4,21] Sparfloxacin inhibited these organisms at 8 mg/L and clinafloxacin at 1 mg/L.

Among other reported organisms of interest, *Corynebacterium diphtheriae* was susceptible to ciprofloxacin, with an MIC_{90} of 0.12 mg/L. Against the same organism, trovafloxacin was more potent with an MIC_{90} of 0.06 mg/L.[15] Likewise, with only a few isolates studied, *Bacillus cereus* strains appear to be quite susceptible to ciprofloxacin and trovafloxacin (MIC_{50} = 0.008 to 0.03 mg/L), and to LB 20304 ($MIC_{50} \leq 0.004$ mg/L).[5,7]

5. Conclusions

Several of the new fluoroquinolones described here demonstrate high potency against Gram-positive organisms, including strains resistant or relatively resistant to the older generation of fluoroquinolone antimicrobials. Nevertheless, when one considers fluoroquinolone-resistant strains of *S. aureus* and coagulase-negative staphylococci, the MIC_{90} values of the newer compounds often exceed 1 mg/L, raising questions as to the applicability of these new compounds in infections caused by such organisms. Likewise, for the problem pathogen *E. faecium*, while the newer agents demonstrate greater potency than older fluoroquinolones, the resulting inhibitory concentrations often exceed 8 mg/L. A notable exception in this regard was sitafloxacin, which inhibited 90% of strains at concentrations between 0.78 and 2 mg/L. At the present time, it is not known whether new agents with inhibitory concentrations falling into a 'susceptible' range will prove effective in clinical use against strains that are highly resistant to the older fluoroquinolone compounds. In addition, it is hoped that utilisation of compounds with the greatest potency against staphylococci, streptococci, and enterococci will minimise the likelihood that resistance will emerge. With respect to clinical practice, this is also an unproven hypothesis.

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