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SESSION 2

Laboratory Survey of Fluoroquinolone Activity

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Fluoroquinolones are active against a wide variety of bacteria. The antibacterial spectra of fluoroquinolones encompass staphylococci, *Bacillus* species, and *Corynebacterium* species implicated in infections of the immunocompromised host; Enterobacteriaceae; most intestinal pathogens; and many gram-negative organisms commonly causing nosocomial infections. *Haemophilus influenzae*, *Haemophilus ducreyi*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Branhamella catarrhalis* are highly susceptible to this class of drugs. Because of their ability to penetrate into phagocytes, fluoroquinolones have been tested against intracellular pathogens: *Legionella* species, *Rickettsia conorii*, *Rickettsia rickettsii*, and *Brucella melitensis* are very sensitive; *Chlamydia trachomatis* and the mycoplasmas are borderline; and some antimycobacterial activities deserve further investigation. Species that are generally resistant include *Pseudomonas maltophilia*, *Pseudomonas cepacia*, *Pseudomonas pseudomallei*, *Alcaligenes* species, *Nocardia* species, *Bordetella bronchiseptica*, and most anaerobes.

All quinolones are structurally related to nalidixic acid, but the new generations of these drugs have an antimicrobial potential that is substantially enhanced in comparison with that of the parent compounds. Here we review the antibacterial spectrum of the newer quinolones as it has been described in the literature issued since the First International Symposium on New Quinolones in July 1986. Data on MIC_{90} values for the fluoroquinolones are summarized in table 1.

Gram-Positive Cocci

Fluoroquinolones are generally active against staphylococci, and there is no cross-resistance with other groups of antibiotics. This activity encompasses both methicillin-susceptible and methicillin-resistant strains of *Staphylococcus aureus* [1–6], *Staphylococcus epidermidis* [1, 6, 7], *Staphylococcus haemolyticus* [1, 7], *Staphylococcus hominis*, and *Staphylococcus saprophyticus*. Ciprofloxacin [8, 9] and enoxacin [10] have been found to be as efficacious as vancomycin for the treatment of experimental endocarditis caused by methicillin-resistant *S. aureus*. However, resistance can emerge during therapy for staphylococcal infection with a fluoroquinolone, as has clearly been shown in a smiliar model [11]. Fluoroquinolones express weaker activity against streptococci, whatever the species considered [4, 5, 12–14]; this observation has been confirmed in experimental enterococcal endocarditis, which was less effectively treated with ciprofloxacin than with procaine penicillin [15]. MIC_{90} values for commonly used fluoroquinolones against streptococci are typically ≥1 mg/L, but newer compounds such as A-61827 have shown improved antistreptococcal activity [16]

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Gram-Positive Bacilli

Fluoroquinolones have been tested against various difficult-to-treat gram-positive bacilli that are increasingly implicated in severe infections of the immunocompromised host. In tests with *Listeria monocytogenes*, MIC_{90} values exceed the cutoff point for susceptibility to fluoroquinolones in most cases, but there are notable exceptions with ciprofloxacin and ofloxacin [4, 5, 17]. More potent activities have been reported against *Corynebacterium species* [18], including strains of group D2 [19, 20] and group JK [17, 21]. *Bacillus* species [17, 22], and notably the pathogenic *Bacillus cereus* [22], are within the spectrum of activity of ciprofloxacin.

Activity against *Nocardia asteroides* varies widely from strain to strain [4, 23, 24]. Although most isolates seem inaccessible to the fluoroquinolones, oc-

Table 1. In vitro activity of three quinolones as reported in the recent literature (July 1986 through July 1988).

Organism	Reported range of MIC_{90} values (mg/L)			Reference(s)
	Cpfx	Ofx	Pfx	
Acinetobacter species	0.06–1	1	1	4, 5, 37, 49
Aeromonas hydrophila	0.008–0.06	0.015	0.06	5, 53
Agrobacterium species	0.06	0.5	0.25	5
Alcaligenes species	2–16	4–32	8–32	5, 37, 58
Bacillus species	0.2–1	. . .	. . .	17, 22
Bacteroides species	4–>64	4–64	>64	25, 59–62
Bordetella bronchiseptica	0.5–4	8	2	35, 37
Bordetella parapertussis	<0.06	0.12–0.25	. . .	35
Bordetella pertussis	0.12	0.5	. . .	35, 36
Branhamella catarrhalis	0.015–0.03	. . .	0.25	4, 34
Brucella melitensis	0.5–0.8	0.8	6	84, 85
Campylobacter jejuni/coli	0.25–1	0.25–2	2	5, 6, 42
Capnocytophaga species	0.06–0.12	0.25–0.5	0.5	54, 55
Chlamydia trachomatis	1–1.56	1.56	. . .	76–80
Citrobacter diversus	0.03–0.06	. . .	. . .	4, 44, 49
Citrobacter freundii	0.015–0.25	0.25	1	4, 5, 44, 49
Clostridium species	1–8	8–>64	. . .	59, 60
Corynebacterium, group D2	1	0.25–0.5	. . .	3, 19, 20
Corynebacterium, group JK	1–16	. . .	. . .	17, 21
Enterobacter cloacae	0.06–0.12	0.25	. . .	4, 6, 49
Enterobacter species	0.03–0.12	0.5	1	4, 5, 49
Escherichia coli	0.03–0.6	0.06	0.125–0.25	4, 5, 25, 49
Fusobacterium species	8–16	. . .	>64	25
Gardnerella vaginalis	4	. . .	32	25, 80
Haemophilus ducreyi	<0.06	. . .	<0.06	25, 29
Haemophilus influenzae	0.008–0.03	0.015–0.03	0.03	4–6, 30
Klebsiella pneumoniae	0.06–0.24	0.25	. . .	3, 4, 49
Klebsiella species	0.06–0.12	0.25	0.5	3, 45, 49
Legionella species	0.125	0.06	. . .	72
Listeria monocytogenes	0.5–3	2	8	4, 5, 17
Mobiluncus species	4	. . .	32	25
Moraxella species	0.5	. . .	2	37
Morganella morganii	0.03	0.125–0.25	0.5	4, 5, 6, 49
Mycobacterium avium complex	2–50	8–50	. . .	63, 64, 66–69
Mycobacterium chelonae	4–25	100	. . .	64, 70
Mycobacterium fortuitum	0.25	0.4	. . .	64, 70
Mycobacterium kansasii	2	2–3	. . .	64, 67
Mycobacterium marinum	0.8–2	6	. . .	64, 70
Mycobacterium scrofulaceum	>8	25	. . .	64, 70
Mycobacterium tuberculosis	0.5–1	0.8–1	. . .	63–67, 70
Mycobacterium ulcerans	0.5	. . .	. . .	64
Mycoplasma species	1–8	. . .	. . .	80, 81
Neisseria gonorrhoeae	0.002–0.03	0.015–0.03	. . .	6, 26, 28
Neisseria meningitidis	0.004	0.015	0.03	4, 5
Nocardia asteroides	8	16–64	64	5, 23
Peptococcus species	4–8	16	. . .	60, 61
Plesiomonas shigelloides	0.008	0.015	0.06	5
Propionibacterium species	4–64	4	. . .	60
Proteus mirabilis	0.12	0.25	. . .	3, 4, 49
Proteus species (indole-positive)	0.03–0.06	0.25–2	0.25	3–6, 49
Providencia species	0.06–8	1	0.25	4, 5
Pseudomonas aeruginosa	0.25–2	2	2–4	4–6, 21, 37, 48, 49
Pseudomonas cepacia	2–4	16	8	4, 6, 37
Pseudomonas fluorescens	0.25–1	8	4	4, 6, 37, 48
Pseudomonas maltophilia	1–16	4–8	2–4	4, 5, 37, 48, 49, 51
Pseudomonas pseudomallei	8	8–32	. . .	6, 52

(*continued*)

Table 1. *(continued)*

Organism	Reported range of MIC_{90} values (mg/L)			Reference(s)
	Cpfx	Ofx	Pfx	
Pseudomonas putida	0.25–4	8	. . .	6, 48
Pseudomonas stutzeri	0.5	. . .	1	37
Salmonella species	<0.015–0.25	<0.06	0.25	4–6
Serratia marcescens	0.125–1	0.25–2	1	4–6, 49
Shigella species	<0.015–0.03	0.06–0.12	0.06–0.12	4–6, 39
Staphylococcus aureus (methicillin-sensitive)	0.4–1	0.5–2	0.5–1	1, 4–6, 17, 49
S. aureus (methicillin-resistant)	0.25–1	0.4–>16	0.5–1	1, 2, 4–6, 17, 49
Staphylococcus epidermidis	0.25–1	0.25–0.5	1	1, 4–7
Staphylococcus haemolyticus	0.5–1	0.5	0.5	1, 4, 7
Staphylococcus hominis	1	0.5	1	1, 4
Staphylococcus saprophyticus	0.5–1	1	4	1, 4, 5
Streptococcus faecalis	0.5–2	2	4	4, 5, 14, 49
Streptococcus mitis	2	. . .	. . .	4
Streptococcus pneumoniae	1	1	8	4, 5
Streptococcus salivarius	2	. . .	. . .	4
Streptococcus sanguis	0.25	. . .	. . .	4
Streptococcus species, group A	2	. . .	. . .	4
Streptococcus species, group B	0.5–4	1	16	4, 5, 12
Streptococcus species, group C	2	. . .	. . .	4
Streptococcus species, group G	1–2	. . .	. . .	4, 12, 13
Ureaplasma urealyticum	4–8	. . .	. . .	80, 81
Vibrio parahaemolyticus	0.06	0.5	. . .	6
Yersinia enterocolitica	0.03	<0.06–0.12	0.25	4–6

casional strains appear to be susceptible in vitro to ciprofloxacin [5, 23], ofloxacin [5, 23], pefloxacin [5], and/or enoxacin [24].

Gram-Negative Genital Pathogens

Fluoroquinolones show extremely potent activity against *Neisseria gonorrhoeae* [25–28] and *Haemophilus ducreyi* [25, 29], with no cross-resistance to other groups of antibiotics, notably the penicillins. In contrast, *Mobiluncus* species are always resistant [25], and *Gardnerella vaginalis* does not appear susceptible in most cases [25].

Gram-Negative Respiratory Pathogens

Fluoroquinolones are potent inhibitors of *Haemophilus influenzae* [4–6], including β-lactamase-producing strains [6, 30], β-lactam-tolerant strains [30], and multiresistant isolates [31]. In murine pneumonia caused by *H. influenzae*, ciprofloxacin [32], enoxacin [33], and ofloxacin [33] produced more intrapulmonary killing than did ampicillin. *Branhamella catarrhalis* is also highly susceptible to newer quinolones [4, 34], and this susceptibility is independent of β-lactamase production [34]. With regard to *Bordetella* species, *Bordetella pertussis* is most susceptible [35, 36]; MIC_{90} values are two- to fourfold higher against *Bordetella parapertussis* [35]; and most strains of *Bordetella bronchiseptica* are resistant [35, 37].

Gram-Negative Intestinal Pathogens

Potent activities against aerobic or microaerophilic enteropathogens have been reported. Besides the well-recognized activity against *Escherichia coli* [38], multiresistant *Shigella* species have been consistently susceptible to fluoroquinolones [39]. The antibacterial spectrum of fluoroquinolones also encompasses *Yersinia enterocolitica* [4–6, 38], *Aeromonas hydrophila* [5, 38], *Plesiomonas shigelloides* [5, 38], *Vibrio parahaemolyticus* [6], and most *Salmonella* species [4, 5] (including ampicillin- and chloramphenicol-resistant strains [6]). Ciprofloxacin consistently cured lethal *Salmonella typhimurium* infection in immunocompromised mice, whereas ampicillin or chloramphenicol did not [40]. Higher MIC_{90} values have been shown against *Campylobacter jejuni*, *Campylobacter coli* [5, 38, 41, 42], and *Campylobacter pylori* [43]. A majority of these strains can be considered susceptible, but occasional resistance has been encountered.

Gram-Negative Nosocomial Organisms

Most nosocomial Enterobacteriaceae – notably *Klebsiella* species, *Enterobacter* species, *Citrobacter* species, *Providencia* species, *Proteus* species, *Morganella morganii*, and *Serratia marcescens* – are inhibited by readily achievable fluoroquinolone concentrations [4–6, 44]. This susceptibility is seen in organisms that are resistant to penicillins, cephalosporins, and aminoglycosides. There are clear exceptions among these strains, however, [5, 45, 46], and resistance may become an increasing concern in the future if fluoroquinolones are widely used in hospital practice.

For *Pseudomonas aeruginosa* [4–6, 47–49], MIC_{90} values are generally higher than those for Enterobacteriaceae; the activity of compounds such as norfloxacin is too weak for clinical use except in urinary tract infections. Ciprofloxacin, which is the most effective quinolone against *P. aeruginosa*, generally exhibits MICs within the susceptible range, but resistance can occur during therapy, as has been shown in a murine model [50]. With regard to other *Pseudomonas* species, the activity of fluoroquinolones is variable. MIC_{90} values for *Pseudomonas fluorescens* and *Pseudomonas stutzeri* [48] are similar to those for *P. aeruginosa*, while *Pseudomonas maltophilia* and *Pseudomonas cepacia* [4, 48, 51] are more resistant. A non-nosocomial *Pseudomonas* species, *Pseudomonas pseudomallei* (which is responsible for melioidosis), should be considered resistant [52].

Fluoroquinolones are highly active against *Aeromonas hydrophila* [5, 38, 53], *Plesiomonas shigelloides* [5, 38], *Capnocytophaga* species [54, 55], *Agrobacterium* species [5], and dysgonic fermenter 2 [56]. Higher MIC_{90} values (but still below the cutoff point for susceptibility) have been reported for a majority of *Acinetobacter* species [5, 46, 49, 57]. *Alcaligenes denitrificans* [5, 58] should be regarded as resistant.

Strict Anaerobic Bacteria

Most clinically important anaerobes, such as *Bacteroides fragilis* or *Clostridium* species are resistant to presently marketed fluoroquinolones [25, 59–62]. Although ciprofloxacin is active in vitro against some anaerobes (e.g., *Bacteroides ureolyticus* and some anaerobic cocci), this activity is too aleatory for the empiric treatment or the prophylaxis of anaerobic infections [59]. Newer, apparently more potent antianaerobe compounds, such as A-61827 [16], may be proven more effective in the future.

Special Intracellular Bacteria

Therapy for infections caused by intracellular bacteria is often difficult because the pathogens in situ cannot be properly inhibited by the intracellular concentrations actually achieved by the most potent antibiotics. Hence treatment schedules are prolonged, adverse reactions are aggravated, and drug resistance emerges easily. Since the fluoroquinolones are known to be taken up by the host's phagocytic cells, their potential uses for the treatment of intracellular infections have aroused much interest. For *Mycobacterium hominis*, MIC_{90} values of ciprofloxacin [63–66], ofloxacin [65–67], and fleroxacin [64] were found to be significantly lower than the peak serum levels produced by these agents. In the case of ciprofloxacin and ofloxacin, synergistic effects with rifampin and isoniazid were demonstrated [65]. Clearly, these in vitro findings deserve further clinical studies. MICs for the *Mycobacterium avium* complex [63, 64, 66–69], *Mycobacterium xenopi* [64], *Mycobacterium scrofulaceum* [64, 70], and *Mycobacterium chelonae* [64, 70] are higher and probably not achievable by therapy, but other potentially susceptible atypical mycobacteria may include *Mycobacterium kansasii*, *Mycobacterium fortuitum*, *Mycobacterium ulcerans*, and *Mycobacterium marinum* [64, 69, 70]. Fluoroquinolones have also been tested against *Mycobacterium leprae* by measurement of intracellular ATP decay after direct in vitro exposure to antimicrobial agents [71]. In this system, ciprofloxacin showed some activity – lower than that exhibited by conventional antileprosy drugs, however.

Legionellosis represents a potential target for fluoroquinolones. In vitro all species of *Legionella* have been highly susceptible to ciprofloxacin, ofloxacin, enoxacin, and norfloxacin [72]. In a system using peripheral human monocytes, fluoroquinolones inhibited the growth of intracellular *Legionella pneumophila* at concentrations readily achievable in serum [73]. In experimental legionellosis, ciprofloxacin [72, 74] or pefloxacin [75] performed similarly to or better than the reference antibiotic, erythromycin or rifampin. Further clinical studies are now in progress.

Against *Chlamydia trachomatis*, ciprofloxacin [76–80], ofloxacin [77, 78], fleroxacin [78], lomefloxacin [78], and other investigational quinolones [78, 80] have shown inhibitory activity at concentrations attainable in serum. The standard drugs tetracycline and erythromycin, however, are more active on a weight-for-weight basis, and the actual role of quinolones in therapy for chlamydial infections has yet to be determined. Newly developed quinolones such as T-3262 [78] display an especially low MIC_{90} against *C. trachomatis* and may deserve special consideration in further clinical investigations.

Several quinolones, including ciprofloxacin, exhibit some activity against *Mycoplasma hominis*, *Mycoplasma pneumoniae*, and *Ureaplasma urealyticum* [79–81]. These observations also require clinical evaluation.

Two studies suggest that ciprofloxacin and pefloxacin may be useful in rickettsiosis. These compounds were effective in vitro and in ovo against *Rickettsia conorii* and *Rickettsia rickettsii* [82, 83]. Ciprofloxacin, ofloxacin, and pefloxacin were also active against *Brucella melitensis* [84, 85].

New Fluoroquinolone Compounds

More recently developed compounds, such as fleroxacin [86–88], difloxacin [89–91], A-56220 [89–91], and lomefloxacin [92], display the typical features of the antibacterial activity of previous fluoroquinolones. Other compounds, notably T-3262 [93], CI-934 [94], S-25930 [95], S-25932 [95], E-3846 [96], and temafloxacin [97, 98], show somewhat improved activity against gram-positive organisms (including *S. aureus*). PD 127,391 exhibits more potent activity against *C. trachomatis* or anaerobes [99].

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