Fluoroquinolones and Anaerobes

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The usefulness of fluoroquinolones for the treatment of mixed aerobic and anaerobic infections has been investigated since these agents started being used in clinical practice. Newer compounds have increased in vitro activity against anaerobes, but clinically relevant susceptibility breakpoints for these bacteria have not been established. Pharmacodynamic analyses and corroboration by new data from clinical trials have enhanced our knowledge concerning the use of fluoroquinolones to treat selective anaerobic pathogens. These studies suggest that newer agents could be useful in the treatment of several types of mixed aerobic and anaerobic infections, including skin and soft-tissue, intra-abdominal, and respiratory infections. The major concerns with expanding the use of fluoroquinolones to treat anaerobic infections have been reports of increasing resistance in Bacteroides group isolates and the impact of these antibiotics on the incidence of Clostridium difficile–associated disease.

Since the introduction of ciprofloxacin, there has been continuing interest in the ability of fluoroquinolones to treat infections involving anaerobic bacteria [1]. Ciprofloxacin lacked in vitro potency against many important anaerobic bacteria, but several newer quinolones looked promising [2–6]. Trovaflxacin was the first fluoroquinolone to receive approval from the US Food and Drug Administration for the treatment of anaerobic bacteria, such as Bacteroides fragilis, Peptostreptococcus species, and Prevotella species isolated from patients with intra-abdominal and pelvic infections [7, 8]. Levofloxacin and sparfloxacin are not as potent as trovafloxacin in vitro but possess good activity against selective anaerobic bacteria [9, 10]. The potential of levofloxacin to treat infection due to anaerobes based on in vitro and pharmacodynamic studies, as well as data from clinical trials, has recently been reviewed [11].

The methoxyfluoroquinolones, gatifloxacin and moxifloxacin, have in vitro potency similar to that of trovafloxacin against a broad spectrum of anaerobic bacteria and appear to have the potential to treat mixed aerobic and anaerobic infections [12–14]. Moxifloxacin recently received approval from the US Food and Drug Administration for the treatment of complicated skin or skin-structure infections and complicated intra-abdominal infections. Other compounds, such as gemifloxacin and garnoxin, have potent in vitro activity against anaerobes, but their clinical usefulness against these bacteria is currently unknown [15–17].

MICROBIOLOGICAL ACTIVITY

Variation in the susceptibility of anaerobes can be the result of differences in geography, site of infection, and clonal populations, as well as regional antimicrobial use patterns. In addition, the in vitro activity of fluoroquinolones against anaerobes can vary depending on the drug, pathogen, and animal origin [11]. For example, all of the newer agents exhibit good activity against common anaerobic bacteria isolated from the respiratory tract (e.g., Peptostreptococcus, Fusobacterium, and Prevotella species) but are considerably less active against intra-abdominal isolates (e.g., B. fragilis group) [18, 19]. Furthermore, selective anaerobes (e.g., Fusobacterium species) isolated from animal bite wounds can exhibit much higher MICs than do similar isolates recovered from human bite infections [20].

Periodontal infections. The in vitro activity of moxifloxacin has been studied against anaerobic bacteria isolated from odontogenic abscesses and periodontal infections [21, 22]. The MIC₉₀s were <0.5 μg/mL for anaerobic isolates from periodontal infections, which included Porphyromonas gingivalis, Prevotella species, Actinomyces species, Fusobacterium nucleatum, and Peptostreptococcus species. Similar findings were reported for odontogenic abscesses.

Respiratory infections. Goldstein and colleagues [18, 23] have published a number of studies about the activity of various agents against isolates obtained via antral sinus puncture in...
patients with sinusitis. Overall, the newer fluoroquinolones were found to be highly active against anaerobic bacteria, including *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* species, with a majority of isolates requiring MICs of <1.0 µg/mL (table 1).

**Bite wounds.** Goldstein et al. [20, 28, 29] have performed studies of several fluoroquinolones against a wide variety of anaerobic bite wound isolates. In general, newer fluoroquinolones are quite active against bite wound isolates, with the exception of *Fusobacterium nucleatum*, a newly described species isolated from dog and cat bite wounds that was found to be intrinsically fluoroquinolone-resistant (MIC, >4 µg/mL). *Fusobacterium russia*, a veterinary isolate found in infected human bite wounds, also exhibits fluoroquinolone resistance, with all isolates tested requiring MICs of >8 µg/mL. *Bacteroides tectum* is consistently susceptible to these newer agents at <0.25 µg/mL, whereas *Bacteroides ureolyticus* group isolates often require >2 µg/mL for inhibition. Unique isolates from animal bite wounds, such as *Porphyromonas macaccae*, *P. gingivalis*, and *Prevotella heparinolytica*, are usually susceptible to these antibiotics at <0.5 µg/mL. *Veillonella* species isolates usually have MIC90s of 0.5 µg/mL against newer fluoroquinolones. Most *Peptostreptococcus* species and other *Porphyromonas* and *Prevotella* species tested required <4 µg/mL levofloxacin for inhibition.

**Skin and soft-tissue infections.** In vitro analysis by Wexler et al. [10] of 175 anaerobic bacteria isolated from skin and soft-tissue infections revealed that levofloxacin inhibited 73% of these isolates at 2 µg/mL. Goldstein et al. [30] reported on the susceptibility of 113 isolates from 25 consecutive cases of diabetic foot wound infection being treated at the hospital. Of the 22 anaerobe isolates recovered from these patients, all *Peptostreptococcus* species were susceptible to levofloxacin (MIC, <4 µg/mL). Resistance (MIC, >4 µg/mL) was found in isolates of *B. fragilis*, *Bacteroides ovatus*, and *Prevotella* species. In a study of 550 anaerobe isolates from patients with surgical infections, including diabetic foot infections, moxifloxacin inhibited 97% of these isolates at <4 µg/mL [27]. Against *B. fragilis*, moxifloxacin’s MIC90 was 1.0 µg/mL. Against other *Bacteroides* species, the MIC90 was 2–4 µg/mL. Moxifloxacin was least active against *Fusobacterium* species other than *F. nucleatum* (MIC90, 8 µg/mL).

**Intra-abdominal infections.** Citron and Appleman [24] tested 217 anaerobic bacteria recovered from patients with intra-abdominal infections. Trovafloxacin was the most active fluoroquinolone tested, with MICs of <1.0 µg/mL, except against *Fusobacterium* species. The majority of these isolates were inhibited by 4 µg/mL levofloxacin. Moxifloxacin had limited activity against isolates of *Bacteroides thetaiotaomicron* (MIC90, 32 µg/mL) and *B. ovatus* (MIC90, 8 µg/mL). Edminston et al. [27] studied the in vitro activities of moxifloxacin against anaerobic isolates from patients with intra-abdominal and diabetic foot infections. In this study, moxifloxacin’s MIC90 for *B. fragilis* group isolates ranged from 1.0 to 4.0 µg/mL. The MIC90 of this fluoroquinolone for isolates of *B. thetaiotaomicron* and *B. ovatus* was 2.0 µg/mL. Aldrich and Ashcroft [31] found that 373 (91%) of 410 anaerobes tested were susceptible to <2

Table 1. Comparative in vitro activity of newer fluoroquinolones against common anaerobic pathogens.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Levofloxacin</th>
<th>Gatifloxacin</th>
<th>Moxifloxacin</th>
<th>Gemifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteroides species</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>Bacteroides fragilis</em></td>
<td>1.0</td>
<td>4.0</td>
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<td>0.5</td>
</tr>
<tr>
<td><em>Bacteroides thetaiotaomicron</em></td>
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<td>16.0</td>
<td>...</td>
<td>1.0</td>
</tr>
<tr>
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<td>16.0</td>
<td>...</td>
<td>0.5</td>
</tr>
<tr>
<td><em>Bacteroides tectum</em></td>
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<td>0.25</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td><strong>Clostridium species</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
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<td>1.0</td>
<td>...</td>
<td>0.5</td>
</tr>
<tr>
<td><em>Clostridium clostridiforme</em></td>
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<td>16.0</td>
<td>...</td>
<td>8.0</td>
</tr>
<tr>
<td><em>Fusobacterium nucleatum</em></td>
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<td>0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Peptostreptococcus species</strong></td>
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<td>0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Peptostreptococcus micros</em></td>
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<td>0.25</td>
<td>0.125</td>
<td>0.125</td>
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<tr>
<td><em>Peptostreptococcus magnus</em></td>
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<td>0.5</td>
<td>...</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Prevotella species</strong></td>
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<td></td>
</tr>
<tr>
<td><em>Prevotella melaninogenica</em></td>
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<td>1.0</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Prevotella intermedia</em></td>
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<td>0.25</td>
<td>0.125</td>
<td>0.125</td>
</tr>
</tbody>
</table>

**NOTE.** MICs were determined at the R. M. Alden Research Laboratory (Santa Monica, CA).

* At least 10 strains were tested for each organism.
µg/mL moxifloxacin. It was least active against isolates of \textit{B. thetaiotaomicron} and \textit{B. uniformis}. Horn and Robson [32] noted that moxifloxacin had relatively poor activity against 200 \textit{B. fragilis} group isolates (MIC$_{90}$ $8 \mu g/mL$), especially against 22 isolates of \textit{B. vulgatus} (MIC$_{90}$ $64 \mu g/mL$). More recently, Goldstein et al. [33] compared the activity of moxifloxacin with that of several anti anaerobic agents against 923 intra-abdominal isolates. Moxifloxacin was active against 96 (87%) of 110 \textit{B. fragilis} isolates at $<1 \mu g/mL$ and 79 (88%) of 90 \textit{B. thetaiotaomicron} isolates at $<2 \mu g/mL$. Species variation was observed, with \textit{Bacteroides uniformis}, \textit{Bacteroides vulgatus}, \textit{Clostridium clostridioforme}, and \textit{Clostridium symbiosum} being least susceptible and accounting for most of the resistant isolates. Overall, moxifloxacin was active against 763 (83%) of 923 isolates at $<2 \mu g/mL$. Goldstein et al. [34] have also investigated the activity of moxifloxacin against anaerobes isolated from pediatric intra-abdominal infections. Moxifloxacin had in vitro activity against 200 (96%) of these 74 isolates at MICs of $<2 \mu g/mL$. Only 1 isolate of \textit{B. thetaiotaomicron} had an MIC of $4 \mu g/mL$, and 2 isolates of \textit{C. clostridioforme} had MICs of $8 \mu g/mL$. Gatifloxacin has also been studied against a large number of anaerobic bacteria, including those associated with intra-abdominal infections, and exhibited in vitro activity similar to that of moxifloxacin [35]. The overall MIC$_{90}$ for the 351 anaerobes studied was $4 \mu g/mL$; \textit{B. fragilis} group isolates required MIC$_{90}$ of $2.0 \mu g/mL$.

Gemifloxacin was found to be considerably less active than the methoxyfluoroquinolones against many \textit{Bacteroides} group isolates [15]. In this study, the MIC$_{90}$s of this agent against isolates of \textit{B. fragilis}, \textit{B. thetaiotaomicron}, and \textit{B. ovatus} were 2, 16, and $>16 \mu g/mL$, respectively. Gemifloxacin does exhibit in vitro activity as good as or better than that of moxifloxacin against \textit{Peptostreptococcus}, \textit{Porphyromonas}, and \textit{Fusobacterium} species [36].

\textbf{Bacteremia.} Aldridge et al. [37] reported the activity of trovafloxacin against 542 \textit{B. fragilis} group isolates recovered from blood cultures from 12 different US medical centers during 1987–1999. Trovafloxacin exhibited in vitro activity at $\leq 2 \mu g/mL$ against 100% of \textit{B. fragilis} and \textit{Bacteroides distasonis} isolates, 92% of \textit{B. thetaiotaomicron} and \textit{B. vulgatus} isolates, and 90% of \textit{B. ovatus} isolates. \textit{C. difficile} infections. The older fluoroquinolones (e.g., ciprofloxacin and ofloxacin) possess poor in vitro activity against \textit{C. difficile}, with MIC$_{90}$ of $\geq 8 \mu g/mL$ [1, 4]. Levofloxacin also exhibits weak activity against this organism, but trovafloxacin is considerably more potent (MIC$_{90}$ $1.0 \mu g/mL$) [12]. Gatifloxacin and moxifloxacin have similar in vitro activity (MIC$_{90}$ $2 \mu g/mL$) against \textit{C. difficile} [26, 35]. Gemifloxacin exhibits in vitro potency similar to that of trovafloxacin against this organism [28].

\textbf{Time-kill.} The fluoroquinolones exhibit bactericidal activity in both aerobic and anaerobic environments [38, 39]. Killing by fluoroquinolones of some anaerobes, such as \textit{B. fragilis}, can be rapid (6 h) [25, 40]. Bactericidal effects are observed against most anaerobic pathogens by 24–48 h at concentrations that are 2–4 times their respective MIC [25, 40, 41]. In mixed cultures of \textit{B. fragilis} with \textit{Escherichia coli} or \textit{Enterococcus faecium}, the bactericidal activity of trovafloxacin and moxifloxacin against \textit{B. fragilis} was found to be diminished, compared with the activity of these fluoroquinolones against pure cultures of \textit{B. fragilis} [42, 43].

\textbf{Synergy.} Boeckh et al. [44] found no beneficial effect of the combination of ciprofloxacin or ofloxacin with metronidazole and clindamycin in serum against \textit{B. fragilis} and \textit{B. thetaiotaomicron}. Goldstein and Citron [45], using a microbroth dilution method, found that the effect of the combination of ofloxacin and metronidazole was generally additive or indifferent against anaerobic bacteria. No antagonism was found, and there was synergy against isolates of \textit{Clostridium perfringens}. Credito et al. [46] used time-kill tests to study the activity of levofloxacin combined with clindamycin and/or metronidazole and found synergy for 7 of 12 isolates of anaerobic bacteria, which included \textit{B. fragilis}, \textit{B. thetaiotaomicron}, \textit{Prevotella} species, and \textit{C. perfringens}. Conversely, Barry and Brown [47] found that the combination of levofloxacin and metronidazole was only additive or indifferent against various anaerobes. Ednie et al. [48] used checkerboard titrations to test the activity of trovafloxacin in combination with clindamycin or metronidazole against 156 anaerobes. Synergy was observed for only 2 isolates when trovafloxacin was combined with clindamycin but for 7 isolates when combined with metronidazole. All other combinations were additive, and no antagonism was seen.

\textbf{RESISTANCE}

Resistance in the \textit{B. fragilis} group occurs as a result of mutations in \textit{gyrA} and \textit{gyrB} genes, as well as active efflux pumps [49–51]. Mutations in the quinolone resistance–determining regions of \textit{gyrA} can lead to 2- to 8-fold increases in MICs for \textit{B. fragilis} group isolates compared with those of wild-type isolates [49, 52]. Mutations in the quinolone resistance–determining regions of \textit{gyrB} or overexpression of an efflux pump can also play a role in enhancing fluoroquinolone resistance in \textit{B. fragilis} [50, 53]. Clinical isolates of \textit{C. difficile} with decreased susceptibility to fluoroquinolones, recovered from patients in French hospitals, exhibited mutations in either \textit{gyrA} or \textit{gyrB} [54]. Moreover, Ackerman et al. [55] found that 14 of 19 moxifloxacin-resistant isolates of \textit{C. difficile} had mutations in the \textit{gyrA} gene. Mutations in \textit{C. perfringens} have been generated by serial passage in the presence of increasing concentrations of 4 different fluoroquinolones with various activities against anaerobes [56]. Most mutations appeared in the quinolone resistance–determining regions of \textit{gyrA} and \textit{parC} (topoisomerase IV). More mutants with multiple mutations were produced with gatiflox-
acine than with the other fluoroquinolones (norfloxacin, ciprofloxacin, and trovafloxacin) tested.

Increasing fluoroquinolone resistance in Bacteroides species has been observed in several countries. Kato et al. [57] compared isolates of B. fragilis collected in Japan during 1983–1984 with those collected during 1986–1987 against several fluoroquinolones. An increase in MIC ranges was found for the more recent isolates. Antibiotic surveillance testing in the United States between 1995 and 1996, which was before the introduction of trovafloxacin, revealed low-level resistance to trovafloxacin (3.7%–7.3%) among all species in the Bacteroides group [58]. In 1998, the year the drug was launched, the rate of resistance was at 15% and increased to 25% by 2001 [59]. Increasing resistance to newer fluoroquinolones (e.g., trovafloxacin and moxifloxacin) has also been observed in Bacteroides group isolates from fecal samples of healthy people in Madrid [60]. In 1998, trovafloxacin had an MIC of 0.5 µg/mL (range, 0.12–2.0 µg/mL) against 100 Bacteroides group isolates (rate of resistance, 0%). In 2001, moxifloxacin had an MIC of >8 µg/mL against a similar number of organisms. All 12 moxifloxacin-resistant isolates (MIC, >8 µg/mL) were also resistant to trovafloxacin; for 8 isolates, the MICs of both 

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**IMPACT ON ANAEROBIC FLORA**

The quinolones have a selective effect on the normal human intestinal microflora [62]. In healthy volunteers, enterobacteria are strongly suppressed or eliminated during therapy. Newer agents with enhanced in vitro activity against anaerobes have only minor effects on the anaerobic intestinal microflora of healthy subjects [62].

Older fluoroquinolones, such as ciprofloxacin and ofloxacin, were seldom associated with C. difficile infection [63]. Golledge et al. [64] investigated 213 patients receiving ciprofloxacin as monotherapy, and none of the 44 patients being treated for or who later developed diarrhea harbored C. difficile or its toxins. In contrast to these findings, a more recent case-control study showed an association between fluoroquinolone use and risk of C. difficile–associated diarrhea [65]. This study, using multivariable analysis, implicated the use of ciprofloxacin as a risk factor for groups matched for age, sex, and duration of hospital stay. Another matched case-control study conducted by Muto et al. [66] showed a significant association between a large outbreak of C. difficile–associated diarrhea and increased use of levofloxacin. A vast majority of the C. difficile isolates collected were highly resistant to the newer fluoroquinolones. McCusker et al. [67] also identified fluoroquinolone use as a significant risk factor for C. difficile–associated diarrhea in a retrospective multivariable analysis of inpatients in 4 Veterans Affairs medical centers. In a large clinical trial of levofloxacin or β-lactam–based therapy for hospitalized patients with community-acquired lower respiratory tract infection, the incidence of C. difficile–associated diarrhea was 2.2% (11 of 490) among patients treated with levofloxacin and 5.6% (25 of 448) among patients treated with β-lactams [68]. Patients who had previously received antibiotic therapy were significantly more likely to develop C. difficile–associated diarrhea. Khan and Cheesbrough [69] observed a rate of 0.34 cases of C. difficile–associated diarrhea per 1000 occupied bed-days in medical patients with pneumonia or sepsis the year after levofloxacin was introduced. Of note, this incidence of C. difficile–associated diarrhea was ∼30% of the level encountered the prior year, when third-generation cephalosporins were in wide use. A similar finding was observed in a large university-affiliated medical center by Mendez et al. [70]. They evaluated the impact of alternative antimicrobial usage during a shortage of piperacillin-tazobactam. Although a number of changes in antibacterial use were observed, multivariate analysis suggested that the reduced use of ceftriaxone and increased use of levofloxacin correlated with a decreased rate of C. difficile infections.

A study by Gaynes et al. [71] in a long-term care facility observed that an increase in C. difficile–associated diarrhea coincided with a switch from levofloxacin to gatifloxacin. Logistic regression analysis demonstrated associations only between C. difficile–associated diarrhea and use of clindamycin and gatifloxacin. The conversion from gatifloxacin back to levofloxacin in this same facility reduced the incidence of C. difficile–associated diarrhea to its previous level. It is important to note that other infection-control procedures were also introduced before the conversion back to levofloxacin. Of the 43 C. difficile isolates that were available for typing from this facility, all were resistant to gatifloxacin, levofloxacin, and moxifloxacin (MIC, >32 µg/mL). A retrospective study of patients in an acute care community hospital also found a higher incidence of diarrhea after use of gatifloxacin (18.5%) than after use of levofloxacin (12%), but the actual incidence of proven cases of C. difficile–associated diarrhea was low with both fluoroquinolones (2% and 1% for gatifloxacin and levofloxacin, respectively) [72].
PHARMACODYNAMICS

The pharmacodynamic profile of quinolone antibacterial agents has been well elucidated for aerobic bacteria, but data describing their effects against anaerobes are scarce. The free-drug area under the curve at 24 h (AUC₂₄)/MIC ratio is the pharmacodynamic measure that best correlates with efficacy in infection models and in patients [79].

During a recent epidemic of infection due to a hypervirulent strain of C. difficile in Quebec, fluoroquinolones emerged as the most important risk factor for C. difficile-associated diarrhea [73]. Moreover, this strain was found to be highly resistant to ciprofloxacin, moxifloxacin, gatifloxacin, and levofloxacin (MIC, ≥32 μg/mL) [74]. Similar outbreaks involving a hypervirulent, fluoroquinolone-resistant strain of C. difficile have been reported in the United States [75].

Alterations in anaerobic bacteria may also select for vancomycin-resistant enterococci. In a murine model, Donskey et al. [76] found that neither levofloxacin nor ciprofloxacin affected the density of vancomycin-resistant enterococci in stool. Conversely, the methoxyfluoroquinolones (gatifloxacin and moxifloxacin) promoted persistent high-density colonization of stool with vancomycin-resistant enterococci that was significantly higher than that observed in the levofloxacin and ciprofloxacin treatment groups. Similar negative findings in density of colonization have been observed among patients colonized with vancomycin-resistant enterococci who were treated with levofloxacin and ciprofloxacin [77]. In a prospective study of hospitalized patients treated with levofloxacin for community-acquired pneumonia, a lack of colonization with vancomycin-resistant enterococci was observed at day 5 or at discharge if discharge was before day 5 [78].

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In vitro/ex vivo studies. In time-kill experiments of newer fluoroquinolones against a strain of B. thetaiotaomicron, Ross et al. found [80] that AUC/MIC ratios of ≥11 produced a 3-log kill by 14 h. Although this ratio produced bactericidal activity, regrowth occurred after 12 h, and MICs had increased by 4- to 8-fold at 24 h. Higher AUC/MIC ratios were necessary to prevent the occurrence of regrowth and the development of resistance. In follow-up experiments by these investigators, killing of B. fragilis with levofloxacin and trovafloxacin was maximized when an AUC/MIC ratio of ≥40 was achieved [81]. Regrowth did not occur, nor were resistant isolates selected when an AUC/MIC ratio of ≥44 was achieved. Noel et al. [82] studied the antibacterial effects of moxifloxacin against B. fragilis, C. perfringens, and gram-positive anaerobic cocci in an in vitro pharmacokinetic model. Moxifloxacin produced a 2- to 3-log decrease in counts at 24 h against these anaerobes, with AUC/MIC ratios of ≥18. Moreover, there was no evidence of emergence of resistance at these AUC/MIC ratios (table 2).

The pharmacodynamics of levofloxacin combined with various doses of metronidazole (500 mg every 8 h, 1000 mg daily, and 1500 mg daily) have been studied in healthy adults against isolates of B. fragilis (n = 2), B. thetaiotaomicron (n = 1), and Peptostreptococcus asaccharolyticus (n = 1) [83]. Overall, the combination of levofloxacin at 750 mg and metronidazole at 500 mg every 8 h or 1500 mg once daily appeared to have greater bactericidal activity than the regimen with metronidazole at 1000 mg once daily. The combination of 750 mg of levofloxacin plus metronidazole (1500 mg daily) was further investigated against monotherapy with moxifloxacin (400 mg daily) in an in vitro mixed infection model [84]. The combination of levofloxacin plus metronidazole produced very rapid 3-log killing against E. coli and B. fragilis. Moxifloxacin produced a 3-log killing of E. coli and B. fragilis, although not as rapidly. Regrowth of this isolate of B. fragilis did not occur with either fluoroquinolone.

Stein et al. [85] have conducted several ex vivo studies of newer quinolones against anaerobic pathogens by measuring serum bactericidal titers over time. Following a single oral dose (200 mg) of trovafloxacin to healthy volunteers, prolonged (12–24 h) serum bactericidal activity was observed against isolates of B. fragilis (MIC, 0.125 μg/mL), C. perfringens (MIC, 0.094 μg/mL), and Peptostreptococcus magnus (MIC, 0.016 μg/mL).
Against *B. thetaiotaomicron* (MIC, 0.38 μg/mL), serum bactericidal activity was observed only at 2 h. In a similar study, the serum bactericidal activity of gatifloxacin and moxifloxacin against anaerobic respiratory pathogens was investigated [14]. Both of these methoxyfluoroquinolones exhibited bactericidal activity for 12–24 h against the study isolates (*Peptostreptococcus micros, F. nucleatum, P. magnus, and Prevotella melaninogenica*). All of these isolates required MICs of ≤0.5 μg/mL, which would result in free AUC/MIC ratios of ≥40 following a single 400-mg oral dose of these fluoroquinolones in healthy volunteers. High doses of levofloxacin (750 mg) have also exhibited prolonged (12–24-h) serum bactericidal activity against anaerobes such as *C. perfringens, P. magnus, P. melaninogenica*, and *B. fragilis*, with MICs up to 2.0 μg/mL [11].

**Animal models.** Against localized mixed aerobic and anaerobic infections (*Staphylococcus aureus* plus *B. fragilis* or *E. coli* plus *B. fragilis*), Girard et al. [86] found that trovafloxacin was able to significantly reduce colonies of *B. fragilis* (MIC, 0.19 μg/mL) by >1000-fold. In similar experiments, Stearne et al. [8] found that trovafloxacin was able to decrease abscess weight as well as the bacterial counts of *B. fragilis* (MIC, 0.25 μg/mL) after treatment for 5 days. In experimental intra-abdominal abscesses caused by *B. fragilis* (MIC, 0.24 μg/mL) and *E. coli*, trovafloxacin as a single agent was observed to produce survival rates that were comparable to those resulting from treatment with clindamycin plus gentamicin [7]. Onderdonk [87] also studied the effectiveness of trovafloxacin in a rat model of intra-abdominal sepsis. Rats were infected with a cecal inoculum containing aerobic and anaerobic organisms, including *E. coli* and *B. fragilis*. Both trovafloxacin and gentamicin-clindamycin protected animals from lethal infection and abscess formation.

The efficacy of moxifloxacin has been studied in a murine bacteremic model by Schaumann et al. [88]. After intravenous infection of mice with different strains of *B. fragilis* along with a susceptible strain of *E. coli*, survival rates and bacterial contents of organs were recorded following 3 days of treatment with moxifloxacin or imipenem. The MICs of moxifloxacin for the isolates of *B. fragilis* were ≤0.5 μg/mL for 3 isolates and >32 μg/mL for 1 isolate. Overall, mice treated with either drug showed similar improved survival, compared with controls. However, higher colony counts of *B. fragilis* could be recovered from the liver in surviving animals infected with the high-MIC strain of *B. fragilis* following treatment with moxifloxacin.

**CLINICAL TRIALS**

The older fluoroquinolones, most notably ciprofloxacin, have been used to treat mixed aerobic and anaerobic infections, alone and in combination with anti-anaerobic agents [89–93]. In complicated intra-abdominal infections, ciprofloxacin plus metronidazole has been as successful as other treatment regimens, such as imipenem-cilastatin and piperacillin-tazobactam [94–96]. Monotherapy with trovafloxacin was found to be efficacious in the treatment of intra-abdominal and gynecologic infections. In a large, randomized, double-blind clinical trial, trovafloxacin was compared with imipenem-cilastatin to treat hospitalized patients with intra-abdominal infections [97]. Of the 31 patients in the trovafloxacin group with *B. fragilis* isolated at baseline, 30 (97%) were designated as experiencing clinical success. The clinical success rates for patients with infections due to *Peptostreptococcus* species (*n = 15*) and *Prevotella* species (*n = 16*) were 87% and 75%, respectively. Additional cultures identified 15 persistent pathogens that included 2 isolates each of *B. vulgatus* and *Prevotella* species. In a multicenter, randomized trial, trovafloxacin was compared with cefoxitin in patients with acute gynecologic infections, of which the majority had endomyometritis [98]. Clinical success rates by baseline anaerobic pathogen in the trovafloxacin treatment group were 94%, 85%, and 80% for *Prevotella* species, *Peptostreptococcus* species, and *Bacteroides* species, respectively. No anaerobes were recovered from additional cultures for patients who were designated as having experienced clinical failure and who were treated with trovafloxacin.

Yamada et al. [99] studied 24 patients with a variety of gynecologic infections (e.g., endometritis, adenexitis, and abscesses of the Bartholin gland) treated with levofloxacin. They reported a clinical efficacy rate of 96% and superinfection in 2 of 14 bacteriologically evaluable patients but did not report the specific bacteriology of these infections. Levofloxacin has been studied in the treatment of both uncomplicated and complicated skin and skin-structure infections [100, 101]. In a study of complicated skin and skin-structure infections, high-dose levofloxacin (750 mg/day) was compared with ticarcillin-clavulanate [101]. Approximately two-thirds of these infections involved a major abscess. The microbiological eradication rate for obligate anaerobic pathogens was 100% (17 of 17) in the levofloxacin group. These isolates included 4 gram-positive anaerobe isolates (2 each *Peptostreptococcus* species and *Gemella morbillorum*) and 13 gram-negative anaerobe isolates (12 isolates of *Bacteroides* species other than *B. fragilis* and 1 isolate of *Veillonella* species).

In a prospective, randomized, double-blind trial, moxifloxacin (400 mg once daily) was compared with piperacillin-tazobactam followed by amoxicillin-clavulanate in 617 adult inpatients with complicated skin and skin-structure infections [102]. An abscess was documented in ~30% of patients in each group. The rates of bacteriological eradication of anaerobes, such as *Peptostreptococcus, Bacteroides, and Prevotella* species, were 60%, 100%, and 64%, respectively, with moxifloxacin. In a prospective, double-blind, randomized study, moxifloxacin was compared with piperacillin-tazobactam in 681 patients with complicated intra-abdominal infections [103].
to Schering-Plough and have received research grants from all of the man-

B. thetaiotaomicron, 85% for ifloxacin had eradication rates of 85% for

B. fragilis, 81% for B. thetaiotaomicron, 85% for B. uniformis, and 75% for Peptostreptococcus species. Only 3 isolates required MICs of \( \geq 16 \mu g/mL \).

CONCLUSIONS

Our current knowledge suggests that the newer fluoroquinolones could be useful in the treatment of several types of mixed aerobic and anaerobic infections, including respiratory, bite wound, skin and soft-tissue, intra-abdominal, and pelvic infections. One caveat would be animal bites, because veterinary isolates of \( F. canefelimum \) are frequently resistant to fluoroquinolones. The major concern with using fluoroquinolones to treat anaerobes isolated from intra-abdominal infections is the fluoroquinolones' weaker in vitro activity against many \( Bacteroides \) group species other than \( B. fragilis \) (e.g., \( B. thetaiotaomicron \), \( B. uniformis \), and \( B. vulgatus \)). A combination with an antianaerobic agent, such as metronidazole, is warranted for empirical treatment of severely ill patients with complicated pelvic or intra-abdominal infections [104]. The potential for “collateral damage” should also be considered when selecting antimicrobial therapy [105]. Quinolone antimicrobials have now been linked to secondary infections, such as \( C. difficile \)–associated diarrhea, and may lead to increased colo-
nization with vancomycin-resistant enterococci. There is an obvious need for additional clinical trials with the newer fluoroquinolones for mixed aerobic and anaerobic infections, especially in this age of increasing antibiotic resistance [106].

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