Activities of Quinolones Against Obligately Anaerobic Bacteria

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Abstract: Quinolones are of clinical and scientific interest since their discovery based on the nalidixic acid in the early 1960s. They are based on two types of ring structures, the quinolone nucleus and the naphthyridone nucleus. Nalidixic acid as the first discovered agent is a naphthyridone and has only a moderate activity against Gram-negative rods. The modification of the quinolone and naphthyridone structures resulted in increasing activities of the quinolones against Gram-negative, Gram-positive, atypical and obligately anaerobic bacteria and mycobacteria. The quinolones are now divided into four groups due to their different spectrum of activity. The first and second group of quinolones *i.e.* norfloxacin, ciprofloxacin or ofloxacin have no or only little activity against obligately anaerobic bacteria. In contrast, the newer quinolones like sitafloxacin, clinafloxacin, trovafloxacin, moxifloxacin, gatifloxacin, garenoxacin and others like *i.e.* WCK 771 and ATB-492 have significant improved activities against anaerobes. Thus, these quinolones have been considered for the treatment of anaerobe and mixed infections. The present review provides an overview of the activities of quinolones against obligately anaerobic bacteria as described by *in vitro* as well as *in vivo* studies.

Keywords: Quinolones, naphthyridones, anaerobes, aerobe/anaerobe mixed infections.

HISTORY AND CHEMISTRY

Quinolones are of important clinical and scientific interest since their discovery based on nalidixic acid (1-ethyl-7-methyl-4-oxo-1,8-naphthyridin-3-carboxylic acid) in the early 1960s [1]. Nalidixic acid was discovered during research of antimalaria agents, in particular as a by-product during the synthesis of chloroquine [2, 3]. Since then more than 10,000 analogues and derivates have been developed [3-6] and more than 800 million patients have been treated with quinolones [3]. On the topic of quinolones the first two articles mentioned in PubMed were published in 1963. However, the paper of Lesher *et al.* [1] was already published in 1962. Since then, more than 23,000 articles and approx. 2,600 reviews are cited in PubMed. Concerning quinolones and anaerobes approx. 300 articles and approx. 70 review article are recorded.

In contrast to most antimicrobial agents which were first found as products of bacteria or yeasts, the quinolones are synthetic products [2, 7]. They are based on two types of ring structures, the quinolone nucleus and the naphthyridone nucleus [8]. The naphthyridone nucleus has a nitrogen atom at position 8 compared with the quinolone nucleus (Fig. **1**) [8]. Nalidixic acid as the first discovered agent is a naphthyridone and has only a moderate activity against Gram-negative rods [9]. During the 1980s more active compounds were synthesized due to the addition of a fluorine atom at position 6 and a piperazinyl group at position 7 at the quinolone nucleus resulting in *i.e.* norfloxacin, an antimicrobial agent with improving activity against Gram-negative rods. Further modification at the quinolone structures resulted in cipro-
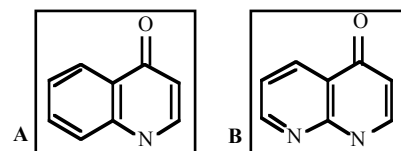

Fig. (1). Quinolone (A) and naphthyridone (B) nucleus.

floxacin and ofloxacin and based on these molecules, a cyclopropyl group at position 1 was introduced in many newer quinolones like gatifloxacin and moxifloxacin (Fig. **2**) [2-9]. Other modification of the basic ring structure resulted in the pyrrolidines, such as *i.e.* clinafloxacin [2, 4, 6-8]. Additional newer compounds like trovafloxacin and gemifloxacin (naphthyridones) based on the naphthyridone nucleus are related to the quinolones (Fig. **2** and **3**) and included in this review [2, 4, 6-8]. Figure **3** shows the development of the quinolones and naphthyridones since the early 1960s as an "evolutionary" tree [4].

The modification of the quinolone and naphthyridone structures resulted in increasing activities of the newer quinolones against Gram-positive, so-called atypical and obligately anaerobic bacteria as well as mycobacteria [3-5, 8, 9-20]. The quinolones are now divided into four different groups due to their spectrum of different activities [21]. Since different classifications have been published the division into the groups or generations is not unequivocal. Furthermore, some authors distinguish subgroups within a group or generation [3, 4, 8, 9, 11-15, 22-24]. In our review, we use the classification into four generations or groups as mentioned by Naber and Adam [21]. The first group of quinolones, *i.e.* norfloxacin and the second group, *i.e.* ciprofloxacin, and ofloxacin have no or only little activity against obligately anaerobic bacteria. Levofloxacin (third group) is the levo-isomer and active component of the chiral molecule ofloxacin and therefore without greater change in the

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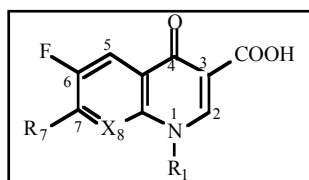
Quinolone pharmacore

Substance	Position R_7	Position X_8	Position R_1	Group
Nalidixic acid (naphthyridone)	CH_3	N	$-CH_2-CH_3$	
Norfloxacin		C-H	$-CH_2-CH_3$	I
Ciprofloxacin		C-H		II
Levofloxacin				III
Grepafloxacin[a] -CH_3 at Position 5		C-H		III
Gatifloxacin[a]		C-OCH_3		IV
Moxifloxacin		C-OCH_3		IV
Trovafloxacin[a] (naphthyridone)		N		IV
Clinafloxacin[a]		C-Cl		IV
Garenoxacin -H at Position 6		C-$OCHF_2$		IV

Fig. (2). Quinolone pharmacore and structures of selected quinolones and two naphthyridones and their relation to the different groups according to Naber and Adam [21].
[a] withdrawn or restricted

spectrum of activity but twice as active as ofloxacin per unit of mass [3, 25]. In contrast, the newer quinolones (fourth group) like sitafloxacin, clinafloxacin, gemifloxacin, garenoxacin, trovafloxacin, moxifloxacin, gatifloxacin and others like *i.e.* WCK 771 and ATB-492 have significant improved activities against obligately anaerobic bacteria [26-50]. Thus, these quinolones have been considered for the treatment of anaerobe and mixed infections. However, due to side effects *i.e.* photosensivity, hepatic- or cardiac-toxicity

some of the quinolones with good anaerobe activity have been withdrawn from the market in some countries or their development has been terminated prematurely. Other quinolones are restricted to the treatment of infections with specific indications [3, 4, 18, 23]. Furthermore, recent data show an emergence of quinolone resistance among *Bacteroides* species [51-53]. In contrast, a good activity of newer quinolones in anaerobe or mixed infections *i.e.* intra-abdominal infections has also been reported [54, 55].
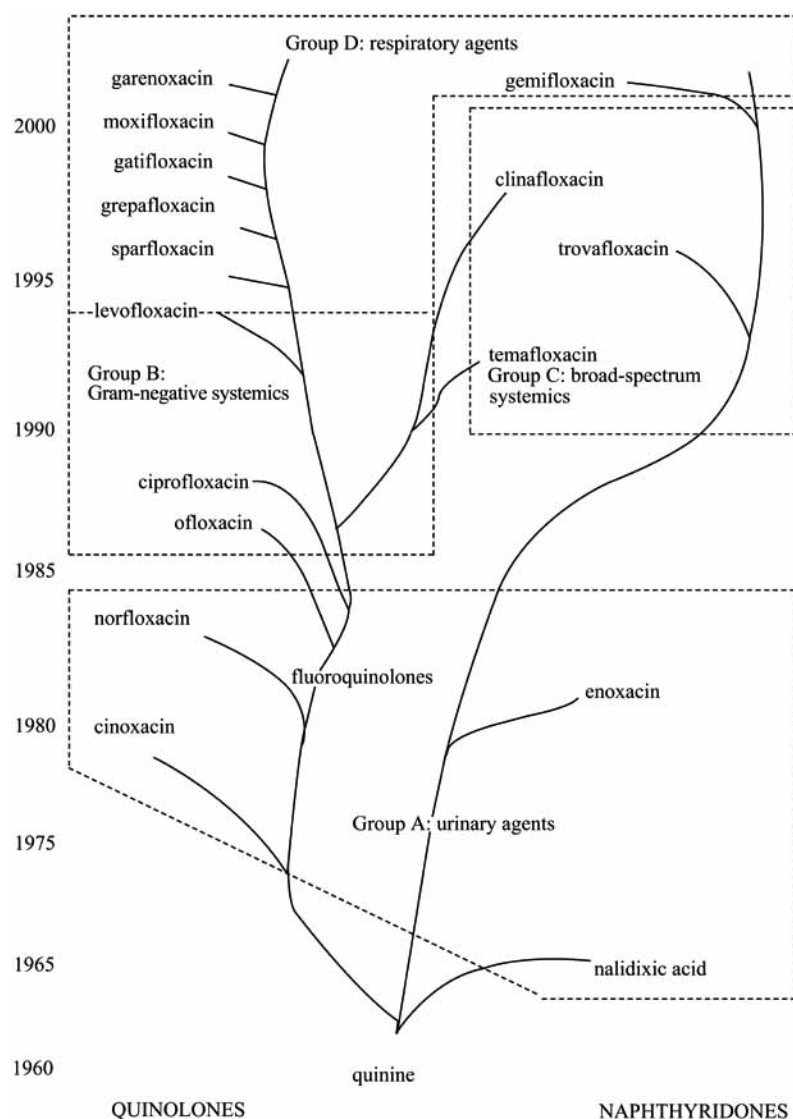
Fig. (3). Development of the quinolones and naphthyridones since the early 1960s as an "evolutionary" tree. (From Andersson, M.I.; MacGowan, A.P. Development of the quinolones. *J. Antimicrob. Chemother.,* **2003,** *51 (Suppl 1)*, 1-11.; with permission).

MECHANISM OF ANTI-ANAEROBE ACTIVITY

DNA topoisomerases are enzymes which are present in prokaryotic as well as in eukaryotic cells. They are necessary for DNA metabolism and the topological structure of DNA, respectively [56]. In both, prokaryotic and eukaryotic cells the DNA topoisomerases are targets for treatment with different drugs, *i.e.* antibacterial drugs or anti-tumor drugs [56, 57]. Different drugs like quinolones, camptothecin and epipodophyllotoxins act on these topoisomerases in the same manner [57]. However, quinolones developed for treatment of infectious diseases in humans have no significant activity against human DNA topoisomerases [2, 56, 57]. There are four different topoisomerases in bacteria (topoisomerase I-IV) that were differentiated in type I and type II topoisomerases [56]. The quinolones interact with one or both type II topoisomerase: DNA gyrase (topoisomerase II) and/or topoisomerase IV. Both enzymes are necessary for the bacteria to replicate their DNA. The bactericidal activity of the quinolones is thus based on the inhibition of this replica-

tion. The DNA gyrase consists of the subunits GyrA and GyrB, whereas the topoisomerase IV consists of the subunits ParC and ParE. Older quinolones in general have greater activity against DNA gyrase than against topoisomerase IV in Gram-negative rods and greater activity against topoisomerase IV than against DNA gyrase in Gram-positive bacteria. Newer quinolones have in general activity against both enzymes [2, 56-63].

As shown in Fig. **4**, the activity of the quinolones against obligately anaerobe bacteria depends on the substituents at position X_8 at the quinolone nucleus as described by Domagala [64]. *I.e.* CCl, CF and COMe as substituents introduce the best activity against anaerobes whereas a nitrogen atom is less active than CH and other substituents *i.e.* CCH_3 are even less active. *I.e.* clinafloxacin and sitafloxacin with a CCl residue at position X_8 have the greatest activities against anaerobes compared to other quinolones. The first and second generations of quinolones have no or little activity. They have in general a CH molecule at position X_8. However,

other substituents must influence the anaerobe activity since trovafloxacin as a naphthyridone has only a nitrogen atom at position X_8 but is much more active against anaerobes as compared with ciprofloxacin with a CH molecule at position X_8. On the other hand, modification at the same position of the quinolone nucleus (X_8) resulted also in different pharmacokinetics and toxicity especially phototoxicity of the quinolones (Fig. **4** and **5**) [64].

MECHANISM OF ANTI-ANAEROBE RESISTANCE

Until today two main mechanisms of resistance of the bacteria against quinolones have been described: alteration of the target enzymes DNA gyrase and topoisomerase IV and reduced concentration of the compounds in the bacteria cells due to reduced permeability and/or increased efflux [61, 62, 65-67]. They are mainly acquired by mutation and chromosomally mediated. However, recently horizontal transfer *via* plasmid has also been reported, which is a great risk for the further spreads of quinolone resistance [68-75]. Both mechanisms of resistance were initially described for aerobically growing bacteria [61, 62, 65-67]. Nevertheless, the mechanisms are also found in obligately anaerobic bacteria [59, 76]. The alteration of the target enzymes are associated in particular with alteration in the quinolone resistance-determining region (QRDR), mainly with amino acid substitution [59, 76, 77]. Oh and Edlund summarized the results of 10 studies investigating alterations in GyrA, GyrB and efflux mechanisms. They reported that alterations in GyrA seem to play an important role in resistance of quinolones against anaerobes. The resistance of strains of the *Bacteroides fragi-lis* group is strongly correlated with amino acid substitutions at positions 82 and 86 in GyrA, which are equivalent to positions 83 and 87 of *Escherichia coli* [59].

Clostridium difficile infections are increasingly associated with quinolone use [78-81]. Hence, the mechanisms of resistance of *C. difficile* need further attention. Ackermann *et al.* reported that twenty-six percent of *C. difficile* strains obtained from patients with *C. difficile*-associated diarrhea were highly resistant to moxifloxacin. The resistance to moxifloxacin in a majority of cases may be due to amino acid substitution in the *gyrA* gene [82]. Furthermore, Rafii *et al.* showed that the efflux of fluoroquinolones appears to be one reason for fluoroquinolone resistance in *C. hathewayi* [83]. Accumulations of quinolones have been described in anaerobic bacteria. However, also in anaerobic bacteria other than *C. hathewayi* efflux mechanisms that exports quinolones have been reported [84-87].

SIDE EFFECTS

As shown by Domagala, the structure-side effect-relationships depends on the substituents on several positions of the quinolone nucleus (Fig. **5**) [64]. However, more serious reactions, *i.e.* the temafloxacin associated hemolytic uremic syndrome or the trovafloxacin-associated hepatitis do not seem to have any specific structural relationship [8]. The so-called "Temafloxacin Syndrome" associated with a hemolytic uremic syndrome was first described during postmarketing surveillance studies and not during clinical trials after temafloxacin treatment [88, 89]. Another adverse side effect
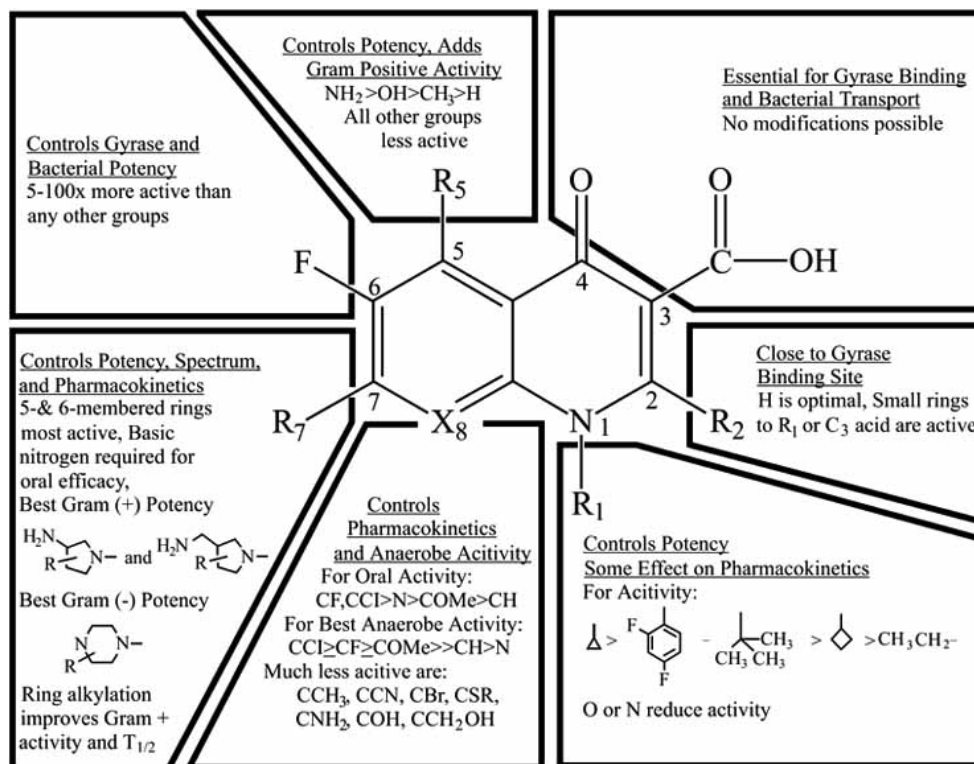

Fig. (4). Antibacterial structure-activity of quinolones. Gram(-), Gram-negative; Gram(+), Gram-positive. (From Domagala, J.M. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J. Antimicrob. Chemother.,* **1994,** *33*, 685-706.; with permission).
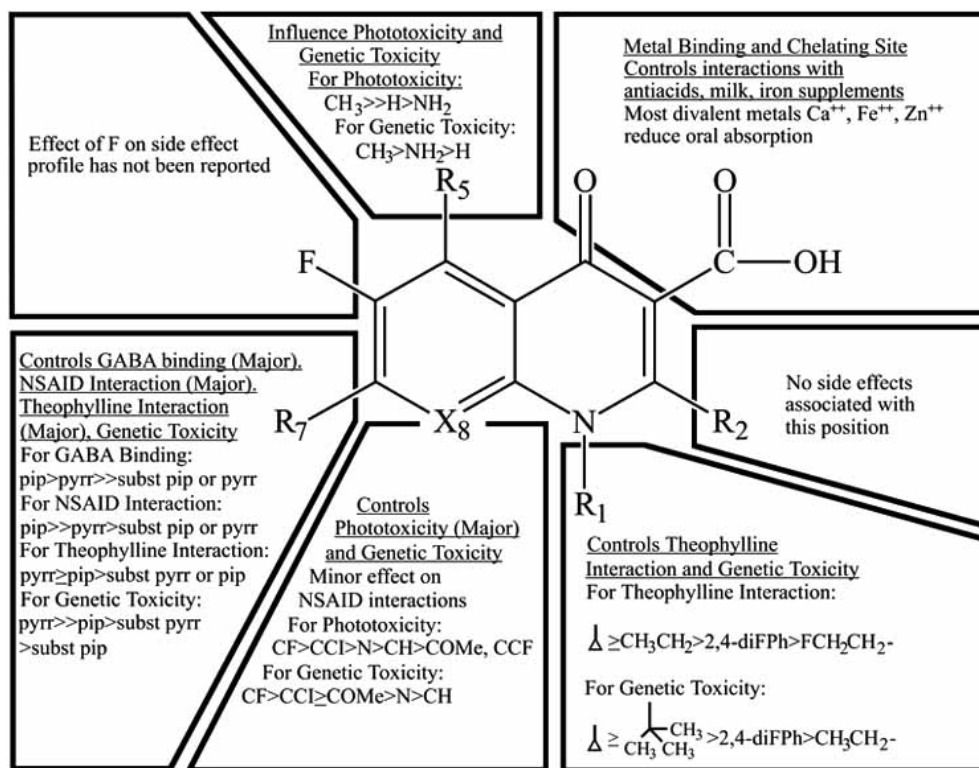
Fig. (5). Structure-sides effects of quinolones. Pip, piperazinyl; pyrr, pyrrolidinyl; diFPh, difluorophenyl. (From Domagala, J.M. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J. Antimicrob. Chemother.,* **1994,** *33*, 685-706.; with permission).

(hepatitis) became even evident during postmarketing surveillance studies after treatment with trovafloxacin [89]. On the other hand, the most common side effects of quinolones are usually mild and involve the gastrointestinal tract, *i.e.* nausea and diarrhea and the central nervous system (headache and dizziness). Other side effects involve the cardiovascular system, musculoskeletal system, endocrine system, and the renal system. However, in general the quinolones are well-tolerated and safe. Nevertheless, due to side effects some of the quinolones with good anaerobe activity, *i.e.* trovafloxacin, clinafloxacin, sitafloxacin, gatifloxacin, and gemifloxacin, have been withdrawn from the market, their development have been terminated prematurely, or are restricted to the treatment of infections with specific indications [3, 4, 18, 23, 88-97].

IN VITRO STUDIES

Several newer fluoroquinolones, *i.e.* moxifloxacin, gatifloxacin, trovafloxacin, clinafloxacin, and sitafloxacin, showed good *in vitro* activity against most anaerobic bacteria when they were first introduced [26-50]. The antibacterial activity of selected quinolones against selected obligately anaerobic bacteria is summarized in (Table **1**). Ciprofloxacin, ofloxacin and levofloxacin are quinolones with no or only low *in vitro* activity against anaerobes. Intermediate *in vitro* activity against obligately anaerobic bacteria has *i.e.* grepafloxacin and gemifloxacin. Improved activity has trovafloxacin, moxifloxacin, and gatifloxacin, whereas sitafloxacin and clinafloxacin have the greatest *in vitro* activity against obligately anaerobes (Table **1**). Ross *et al.* investi-

gated the resistance in anaerobic bacteria following exposure to levofloxacin, trovafloxacin, and sparfloxacin in an *in vitro* pharmacodynamic model. They reported, that MICs increased by fourfold following exposure to levofloxacin at AUC/MIC ratios of 6 and 14, while MICs increased by four- to eightfold following exposure to trovafloxacin and sparfloxacin at AUC/MIC ratios of 11 and 12, respectively [98]. Investigating the pharmacodynamics of trovafloxacin and levofloxacin in an *in vitro* pharmacodynamic model Peterson *et al.* suggests that fluoroquinolones provide antibacterial effects against *B. fragilis* in a concentration-independent manner associated with an AUC_{0-24}/MIC ratio of ≥ 40 [99]. The anti-anaerobe activity of both newer quinolones (WCK 771 and ATB-492), which are currently under investigations, needs intensive scrutiny**.**

At the moment moxifloxacin is the only newer quinolone which is in clinical application without restriction. It is a quinolone that like trovafloxacin, sitafloxacin, clinafloxacin and others belongs to the fluoroquinolone group IV as described by Naber and Adam [21]. Moxifloxacin has like other quinolones of the group IV an antimicrobial activity against many Gram-positive and Gram-negative aerobic and anaerobic bacteria as well as atypical bacteria such as *Chlamydia* and *Mycoplasma* [18, 20, 28, 30, 34, 38, 46, 100, 101]. As indicated by several studies, moxifloxacin has a good *in vitro* activity against important anaerobic bacteria especially *Bacteroides* species [30, 38, 46]. In a recently published study concerning the *in vitro* activity of moxifloxacin against 923 anaerobes, among the *Clostridium* species, only *C. clostridioforme* and *C. symbiosum* were generally

Table 1.   **Activity of Selected Quinolones (MIC$_{90}$, µg/mL) Against Selected Obligately Anaerobic Bacteria (Adapted According to References [26-50])**

Antimicrobial agent	*Bacteroides fragilis*	*Porphyromonas* spp.	*Prevotella* spp.	*Fusobacterium* spp.	*Peptostreptococcus* spp.	*Clostridium* spp.
Ciprofloxacin	2->32	0.5-2	0.5-32	1->16	0.5-8	0.5-64
Levofloxacin	1-32	0.125-4	0.5->16	0.5->32	0.5->16	0.25->16
Moxifloxacin	0.25-8	≤0.03-1	0.125-16	0.125->16	0.125-8	0.125-16
Gatifloxacin[a]	0.5-16	0.25	0.125-16	0.5->8	0.25-4	0.5-4
Grepafloxacin[a]	4	2-4	0.5-16	0.5->16	0.5-4	0.5->16
Gemifloxacin[a]	0.5-4	0.125-1	0.5-16	0.25-2	0.03-4	0.06->16
Trovafloxacin[a]	0.25-8	0.25-1	0.25-8	0.5-8	0.06-1	0.125->16
Sitafloxacin[a]	0.25-1	0.03	0.03-0.25	0.03-0.5	0.03-0.5	0.06-4
Clinafloxacin[a]	0.25-2	0.06	0.125-0.5	0.125	0.06-0.5	0.125-1
Garenoxacin	0.5-4	1	0.25-2	0.25->8	0.25-0.5	1-2
WCK 771	16	--	0.125-8	0.25-16	1	0.25-1
ABT-492	0.12	--	0.03-0.5	0.015	0.004-0.03	0.008

[a] withdrawn or restricted

resistant to moxifloxacin, while all *C. perfringens* and *C. ramosum*, 96% of *C. innocuum*, and 86% of other *Clostridium* species tested were susceptible to ≤2 µg/mL of moxifloxacin. Furthermore, 88% of *B. fragilis* and 86% of *B. thetaiotaomicron* were susceptible to ≤2 µg/mL of moxifloxacin [38].

However, moxifloxacin was the least active agent against 589 *B. fragilis* group isolates comparing to the activities of garenoxacin, clinafloxacin, sitafloxacin, and trovafloxacin [48]. Furthermore, since 1994 fluoroquinolone resistance among *Bacteroides* isolated has markedly increased in the USA. The resistance to trovafloxacin (breakpoint of 8 µg/mL and moxifloxacin (breakpoint of 4 µg/mL) increased from 8% to 25% and from 30% to 43%, respectively [52]. Also in Europe the antimicrobial resistance among *B. fragilis* group isolates is increasing. In a study published in 2003, the MIC$_{90}$ of moxifloxacin was 4 µg/mL and 9% of the 1284 investigated *B. fragilis* group isolates yielded MIC-values ≥8 µg/mL [51]. Furthermore, Noel *et al.* showed that the pharmacodynamics of moxifloxacin against anaerobic bacteria differ from those against aerobes, *i.e. E. coli* [102]. In contrast, moxifloxacin exhibited activity similar to that of levofloaxcin plus metronidazole against a mixed *E. coli* and *B. fragilis* infection in an *in vitro* pharmacodynamic model [103]. However, in another pharmacokinetic/pharmacodynamic study investigating the activity of moxifloxacin against a mixed infection with *E. coli* and *B. fragilis*, moxifloxacin showed only a moderate activity [104].

Conversely, even if sera are obtained 24 h after dosing, a cidal activity of moxifloxacin was found for respiratory pathogens (aerobes and anaerobes). Thus, in the treatment of mixed aerobic-anaerobic respiratory tract infections moxifloxacin may have clinical utility [105]. However, Stein *et. al.* investigated the serum bactericidal activity of moxiflox-

acin and gatifloxacin. If MICs of gatifloxacin were ≥2 µg/mL, they reported little or no serum bactericidal activity of either drug [106]. Nevertheless, moxifloxacin was found to be effective *in vivo* even against a *B. fragilis* strain with high MIC level for moxifloxacin in an experimental animal model of severe mixed aerobe/anaerobic infection [107].

IN VIVO STUDIES

The largest part of the physiologic flora on skin and mucous membranes of humans compromise obligately anaerobic bacteria. As opportunistic pathogens, they often participate in endogenous infections causing mixed infections together with aerobe growing bacteria [108]. A major part of the human colon flora consists of the *B. fragilis* group. This group, in particular *B. fragilis* is frequently involved in anaerobic or mixed aerobic and anaerobic infections, such as intra-abdominal, gynecological, and bloodstream infections [109]. These infections are burdened with high morbidity and mortality and require treatment with antimicrobial drugs showing activity against both aerobic and anaerobic bacteria [108, 110, 111]. The therapeutic potential of the newer quinolones in such infections is under discussion since they showed good *in vitro* activity against most anaerobic bacteria when first introduced [112-114]. Besides *in vitro* studies, newer quinolones *i.e.* trovafloxacin, gatifloxacin, moxifloxacin, and garenoxacin, have shown good activity in anaerobe and mixed aerobe/anaerobe infections in animal models [107, 115-122]. Furthermore, trovafloxacin and clinafloxacin have demonstrated efficacy in the treatment of intra-abdominal infections in clinical studies in humans. Both quinolones were as effective as imipenem/cilastatin in the treatment of intra-abdominal infections [54, 55]. However, due to side effects in post-marketing surveillance studies clinafloxacin have been withdrawn from the market and

trovafloxacin is restricted to the treatment of infections with specific indications.

FUTURE

As shown in a plethora of studies the susceptibility of anaerobic bacteria to antimicrobial drugs is strongly related to certain health care facilities and geographic areas [51, 76, 123-129]. Furthermore, in various countries an increase of resistance to commonly prescribed antibiotics against anaerobe infections *i.e.* clindamycin, cefoxitin and metronidazole has been demonstrated [53, 130-133]. Increasing resistance of anaerobes against imipenem has also been reported [134]. Thus, the knowledge of resistance patterns is of utmost importance for an adequate prophylaxis and treatment even in anaerobic or mixed aerobic and anaerobic infections. Due to the increasing resistance new compounds are necessary for the treatment and prophylaxis of such infections. The data of *in vitro* as well as the *in vivo* studies takes the newer quinolones into consideration for treatment of these infections. However, due to the side effects of various newer quinolones the treatment is restricted in particular. Clinical trials to evaluate the efficacy of moxifloxacin, the only newer quinolone without restriction, in mixed infections were published recently [135]. In this study, moxifloxacin was as efficacy as piperacillin/tazobactam administrated intravenously followed by oral amoxicillin/clavulanic acid in the treatment of complicated intra-abdominal infections. Furthermore, Stein and Goldstein [136] suggest 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. However, because of the data reported in our review, the clinical study data obtained for moxifloxacin treatment of patients with intra-abdominal infections need intensive scrutiny.

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