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Review

# Preserving the efficacy of front-line fluoroquinolones through selective use to optimise clinical outcomes

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ABSTRACT

As antibiotic resistance is increasing worldwide, it is important to prescribe fluoroquinolone (FQ) antibiotics appropriately for a given infection to preserve class efficacy. Clinical studies reveal good efficacy and tolerability of the currently approved FQs (ciprofloxacin, levofloxacin and moxifloxacin) in a wide range of community- and hospital-acquired infections. However, certain features supporting their clinical efficacy suggest a rationale for inclusion of moxifloxacin and ciprofloxacin with complementary clinical benefit on a formulary rather than levofloxacin alone; it may also be more cost-effective. Ciprofloxacin has advantages over levofloxacin in the treatment of Gram-negative infections, whilst moxifloxacin has certain efficacy and ease of use advantages over levofloxacin in respiratory tract infections. To preserve the potential of FQs and to minimise the risk of resistance selection, agents with the highest in vitro activity and supportive pharmacokinetic/pharmacodynamic profiles should be used first-line, as appropriate for local guidelines and prescribing information.



## 1. Introduction

Over the last few decades, fluoroquinolone (FQ) antibiotics as a class gained a key role in the management of a variety of both community-acquired and hospital-acquired infections [1]. Broad-spectrum antibiotics with activity against both Gram-positive and Gram-negative bacteria are useful in many cases, but there is an ongoing recognition that it is essential to use the antibiotic with the highest in vitro activity first to reduce resistance and to improve clinical outcome.

Among many FQ candidates, a few have been stopped or later withdrawn due to toxicity (e.g. cinoxacin, temafloxacin, gemifloxacin, grepafloxacin, sparfloxacin, trovafloxacin, gatifloxacin) (Table 1). These withdrawals have raised concerns regarding the whole antibiotic class, requiring a black-box 'warning and precaution' on the label of the currently approved FQs such as moxifloxacin, levofloxacin and ciprofloxacin. Ciprofloxacin is perhaps the best-known second-generation FQ, with limited activity against Gram-positive pathogens. Third-generation agents, such as levofloxacin, have somewhat improved Gram-positive activity (e.g. against *Streptococcus pneumoniae*). However, the fourth-generation agent moxifloxacin delivered significant improvements against Gram-positive pathogens, including *S. pneumoniae*, atypical organisms and anaerobes, leading to the term 'respiratory quinolone' for both levofloxacin and moxifloxacin [2].

The purpose of this article is to review key features of the currently approved and recommended FQs (moxifloxacin, levofloxacin and ciprofloxacin) in relation to FQ prescribing choices. This paper, however, aims to highlight the reasons why moxifloxacin and ciprofloxacin together on a formulary may be more advantageous than a formulary containing only levofloxacin.

## 2. Complementary antimicrobial coverage

The most frequent community-acquired infections among outpatients are respiratory tract infections (RTIs) and urinary tract infections (UTIs). Early empirical antibiotic treatment is highly recommended against the most likely pathogen(s) to minimise the risk of further complications (e.g. hospitalisation) and/or late clinical failure.

Many community- and hospital-acquired respiratory infections are caused by Gram-positive *S. pneumoniae* and *Staphylococcus aureus*, Gram-negative *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa* and atypical organisms (e.g. *Legionella*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*). It is expected that use of antibiotics selects for resistant isolates either in hospitals or

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**Table 1**
List of approved and withdrawn fluoroquinolones.

| Generation | Withdrawn | Approved |
|---|---|---|
| I | Cinoxacin | Nalidixic acid |
| II | | Ciprofloxacin |
| | | Pefloxacin |
| | | Ofloxacin |
| | | Norfloxacin |
| III | Grepafloxacin | Levofloxacin |
| | Sparfloxacin | |
| | Temafloxacin | |
| IV | Gatifloxacin | Moxifloxacin |
| | Trovafloxacin | Prulifloxacin |
| | | Gemifloxacin |
| | | Sitafloxacin |
| | | Besifloxacin |
| In development | | JNJ-2 |
| | | Delafloxacin |

in outpatient settings. The introduction of earlier FQs such as ciprofloxacin with limited potency against Gram-positive bacteria [1,3,4] probably contributed to the development of FQ resistance in *S. pneumoniae* before the introduction of newer more potent FQs several years later [5]. The Canadian Bacterial Surveillance Network has shown a decrease in FQ resistance in *S. pneumoniae* following the introduction of moxifloxacin [5], which was not seen following the introduction of levofloxacin [5]. Increased minimum inhibitory concentrations (MICs) for *S. pneumoniae* were reported, potentially leading to clinical failures, in the USA in the period 1997–2002 after increased use of levofloxacin [6]. Surveillance data for the period 2007–2011 showed that many pathogens (e.g. *K. pneumoniae*, *S. pneumoniae*, *P. aeruginosa*) remained highly susceptible to these three antibiotics despite general use of various FQs [7]. In Asia, susceptibility to the FQs levofloxacin and moxifloxacin remains >98% in multidrug-resistant (MDR) *S. pneumoniae* isolates [8–10] (Table 2). Certain respiratory pathogens such as *H. influenzae* remained susceptible to FQs [8], whilst others such as *K. pneumoniae* show variable resistance rates between 2% and 23% (Table 3) [8,10,12–22]. In addition, a reduction in the prevalence of ciprofloxacin-resistant meticillin-resistant *S. aureus* (MRSA) isolates was seen in Canadian hospitals [7], probably due to a shift in the prevalence from hospital-associated genotypes to community-associated genotypes [7]. The MOXIAKTIV study has shown that in patients with nosocomial RTIs [10], moxifloxacin was significantly more active than levofloxacin against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

RTIs caused by *P. aeruginosa* are particularly challenging to treat and are a frequent cause of death [23]. Ciprofloxacin still has high activity against *P. aeruginosa* [7,12,18,24,25] and it remains the recommended antipseudomonal FQ to date [26]. In patients with hospital-acquired pneumonia, ciprofloxacin has greater antipseudomonal activity than either moxifloxacin or levofloxacin [23]. Van Eldere reported that the MIC range for the susceptible population is very narrow for all FQs, and for levofloxacin the susceptible *P. aeruginosa* population is placed within two dilutions of the susceptibility breakpoint [23]. Given the possibility of rapid selection of resistant mutants, if insufficient concentrations (e.g. <10× MIC) are used, levofloxacin serum levels of >5 mg/L and <10 mg/L would be needed. Furthermore, FQ resistance of *P. aeruginosa* isolates causing nosocomial infections was correlated more frequently with levofloxacin than ciprofloxacin use [27].

UTIs, which may lead to bacteraemia, are responsible for nearly 10–15% of antibiotic prescriptions in the community [28]. Ciprofloxacin currently tends to be the FQ of choice for the treatment of UTIs compared with moxifloxacin [29,30] or levofloxacin, although FQs in general are facing decreased susceptibility against common UTI pathogens [31]. The most prevalent pathogen in UTIs is *E. coli*, against which ciprofloxacin is still highly active in some countries [19,21]. Although resistance to FQs among *E. coli* isolates, particularly extended-spectrum β-lactamase (ESBL)-producing *E. coli* and other ESBL-producing Enterobacteriaceae (e.g. *K. pneumoniae*), is increasing, and some studies have even found that ciprofloxacin no longer remains active against it [32,33]. Lu et al. have recently found that ca. 50% of ESBL-producing *E. coli* isolates were resistant to both ciprofloxacin and levofloxacin [34]. Other common pathogens causing UTIs include *Proteus mirabilis*, *K. pneumoniae*, *Klebsiella* spp., *Chlamydia* spp. and *P. aeruginosa* [31]. *Pseudomonas aeruginosa* remains rather susceptible to ciprofloxacin, which does not appear to affect the development of resistance in UTIs [27], and a decreased tendency of ciprofloxacin resistance has been reported recently [35].

In complicated skin and skin-structure infections (cSSSIs) the most common pathogens are *S. aureus*, β-haemolytic streptococci (e.g. *Streptococcus pyogenes*, mainly from community-acquired infections), *P. aeruginosa*, enterococci (e.g. *Enterococcus faecalis*), *E. coli* and *Enterobacter* spp. Among the recommended FQs, moxifloxacin is more active than levofloxacin or ciprofloxacin against most of these pathogens [36–39]. Edmiston et al. assessed the activity against 900 surgical aerobic and anaerobic isolates and showed that moxifloxacin was more active than levofloxacin against meticillin-sensitive *S. aureus* (MSSA), *Streptococcus* spp., *Enterococcus* spp., *Enterobacter aerogenes*, *Enterobacter cloacae* and *E. coli* [38]. It was suggested that with its extended spectrum of activity both against aerobes and anaerobes, moxifloxacin may be particularly appropriate for difficult-to-treat infections such as diabetic foot infections (DFIs). This has later been demonstrated in the RELIEF trial enrolling more than 200 DFI patients [39,40].

The aetiology of complicated intra-abdominal infections (cIAIs) is commonly polymicrobial caused by a mixture of aerobic and anaerobic bacteria simultaneously, requiring broad-spectrum antibiotics initially. *Bacteroides fragilis* and other *Bacteroides* spp. are the most commonly isolated causative anaerobes, against which moxifloxacin shows higher activity than levofloxacin [41,42]. Despite widespread use of FQs, susceptibility of the most prevalent *Bacteroides* spp. and other causative pathogens such as *E. coli* in cIAIs remains high to moxifloxacin [41]. According to other studies, moxifloxacin is more active than ciprofloxacin in treating cIAIs [38]; however, in areas with high rates of ESBL-producing and/or FQ-resistant Enterobacteriaceae, susceptibility of the isolated pathogen in cIAIs should be confirmed to avoid clinical failure [43,44].

**Table 2**
Current susceptibility of *Streptococcus pneumoniae* to levofloxacin and moxifloxacin.

| | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | Region |
|---|---|---|---|
| Levofloxacin | 0.5–1.0 | 1.0–2.0 | Asia [8,9] |
| | 0.75 | 1.0 | Europe, Germany [10] |
| | 1.0 | 1.0 | USA [11] |
| Moxifloxacin | 0.064–0.5 | 0.125–0.5 | Asia [8,9] |
| | 0.125 | 0.19 | Europe, Germany [10] |

$MIC_{50/90}$, minimum inhibitory concentration required to inhibit 50% and 90% of the isolates, respectively.