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Abstract

Full Text

Pharmacokinetic/pharmacodynamic target-based dose optimization of quinolones

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ABSTRACT

Quinolones are widely used for the treatment of bacterial infections because of their broad antimicrobial spectrum, favorable tissue penetration, and concentration-dependent bactericidal activity. Optimization of quinolone dosing regimens based on pharmacokinetic/pharmacodynamic (PK/PD) principles is essential for improving clinical efficacy, minimizing toxicity, and limiting the emergence of bacterial resistance. As concentration-dependent antibacterial agents, quinolones are primarily characterized by PK/PD efficacy indices such as ratio of the 24-h area under the concentration-time curve to the minimum inhibitory concentration (AUC24/MIC) and the ratio of peak concentration to MIC (Cmax/MIC), whereas mutant prevention concentration (MPC)-related indices may provide additional insight into resistance suppression. This review summarizes the pharmacokinetic, pharmacodynamic, and PK/PD characteristics of quinolones and highlights the clinical application of PK/PD-guided dose optimization for representative agents, including norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin, and newer quinolones such as nemonoxacin, sitafloxacin, and delafloxacin. The aim is to provide both a theoretical basis and practical guidance for the rational clinical use and individualized dose optimization of quinolones.

Introduction

Since the introduction of nalidixic acid in the 1960s, quinolones have evolved from early non-fluorinated compounds into multiple generations of fluoroquinolones and newer non-fluorinated derivatives, becoming important components of contemporary anti-infective therapy1. Continuous structural optimization has broadened their antibacterial spectrum and improved activity against Gram-negative bacteria, selected Gram-positive bacteria, and atypical pathogens. Owing to their excellent oral bioavailability, extensive tissue distribution, high intracellular penetration, and suitability for intravenous-to-oral switch therapy, quinolones have been widely used in the treatment of respiratory tract infections, urinary tract infections, intra-abdominal infections, skin and soft tissue infections, as well as certain bone and joint infections2–4.

However, the sustained and widespread use of quinolones has also contributed to the increasing prevalence of antimicrobial resistance, particularly among Gram-negative pathogens such as *E. coli*, *P. aeruginosa*, and *Acinetobacter spp.* The emergence of multidrug-resistant strains has exposed the limitations of traditional empirical fixed-dose regimens. In addition, substantial variability among patient populations, infecting pathogens, infection sites, and MIC distributions means that the efficacy of a single dosing regimen is often inconsistent. Inadequate drug exposure may not only lead to clinical failure and incomplete bacterial eradication, but may also prolong the time during which drug concentrations remain within the mutant selection window, thereby promoting the enrichment of resistant subpopulations5,6.

The pharmacokinetic/pharmacodynamic (PK/PD) framework provides a scientific basis for individualized quinolone dosing by linking in vivo drug exposure with antibacterial effect. In recent years, advanced approaches such as population pharmacokinetic modeling and Monte Carlo simulation (MCS) have been increasingly applied in anti-infective research, making PK/PD-guided dose optimization a key strategy for the rational clinical use of quinolones7–10. This review systematically summarizes the pharmacokinetic, pharmacodynamic, and PK/PD characteristics of quinolones, with a particular focus on dose optimization strategies for representative agents across different infection scenarios and special populations, in order to provide a reference for

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precision anti-infective therapy in clinical practice. This review systematically summarizes the pharmacokinetic, pharmacodynamic, and PK/PD characteristics of quinolones, with a particular focus on dose optimization strategies for representative agents across different infection scenarios and special populations, in order to provide a reference for precision anti-infective therapy in clinical practice.

Pharmacokinetic characteristics of quinolones

After oral administration, quinolones are quickly absorbed in the gastrointestinal tract, reaching peak plasma levels in 1–2 h, with bioavailability often between 90% and 100% for Levofloxacin, Moxifloxacin, and Nemonoxacin. Food intake delays absorption and peak concentration time. Except for Delafloxacin, which has a high plasma protein binding rate (about 84%), other drugs have low binding rates (10%–55%). They distribute widely in tissues and fluids, with higher concentrations in the kidneys, liver, lungs, and prostate, enhancing bactericidal effectiveness. Drug metabolism and excretion pathways differ. Most drugs, except Moxifloxacin and Delafloxacin, are primarily excreted unchanged by the kidneys, leading to high urinary concentrations. Additionally, elimination half-lives vary: Ciprofloxacin has short half-lives (3–4 h), while Nemonoxacin, Moxifloxacin, and Sparfloxacin have longer half-lives (11–18 h). Further details are shown in Table 111–19.

Pharmacodynamic and PK/PD characteristics of quinolones

Quinolones are classically categorized as concentration-dependent antibacterial agents. Their bactericidal activity generally increases with rising drug concentrations20, and many agents in this class also exhibit a post-antibiotic effect21, allowing persistent suppression of bacterial growth even after concentrations decline below the MIC. These pharmacodynamic properties distinguish quinolones from time-dependent agents and provide the conceptual basis for the use of exposure-based PK/PD indices in dose optimization.

The PK/PD indices most frequently employed to assess the efficacy of quinolones are the 24-hour area under the concentration-time curve to the minimum inhibitory concentration (AUC_{24}/MIC) and the ratio of peak concentration to MIC (C_{max}/MIC). The PK/PD targets are contingent upon the specific pathogen and the nature of the infection. It is generally recognized that for common respiratory Gram-positive pathogens, such as *S. pneumoniae*, a relatively lower AUC_{24}/MIC target of 30–40 is adequate to achieve favorable therapeutic outcomes22,23. In contrast, for Gram-negative bacteria, such as *Enterobacterales* and *P. aeruginosa*, higher AUC_{24}/MIC targets are typically necessary. Some studies indicate that this target should reach 100–125, with

even higher exposures potentially required in high-inoculum infections, such as bacteremia24,25.

In addition to efficacy, resistance suppression has become a major consideration in quinolone PK/PD evaluation. Concepts such as the mutant prevention concentration (MPC) and the mutant selection window (MSW) have been proposed to describe the relationship between antimicrobial exposure and the selection of resistant subpopulations8,20,26,27. When drug concentrations remain within the MSW for prolonged periods, resistant mutants may be preferentially enriched. Accordingly, dosing strategies that maximize bactericidal exposure while minimizing the duration of concentrations within the MSW may help reduce the probability of resistance emergence, although the clinical translation of these concepts remains more complex than that of conventional efficacy targets. Drawing on these theories, several studies have suggested that the AUC_{24}/MPC and C_{max}/MPC ratios may be more suitable than the traditional AUC_{24}/MIC ratio for accurately reflecting the efficacy of resistance suppression. Nonetheless, both MPC and MSW remain predominantly within the realm of experimental and mechanistic research, with their clinical applicability and standardized implementation currently being limited.

Practical application of PK/PD principles in quinolone selection and dosing optimization

In clinical practice, PK/PD-guided quinolone therapy should not be applied uniformly across all agents in the class. Although quinolones share concentration-dependent antibacterial activity, substantial between-agent differences exist in antimicrobial spectrum, tissue penetration, elimination pathways, PK/PD targets, and susceptibility to host-related pharmacokinetic variability. Accordingly, rational quinolone selection and dose optimization should be individualized on the basis of an integrated assessment of PK/PD targets, pathogen MIC, site of infection, disease severity, and host-specific factors such as renal function and critical illness.

Ciprofloxacin

Ciprofloxacin, a prototypical second-generation fluoroquinolone, has potent activity against Gram-negative bacteria, notably *P. aeruginosa*, and is extensively employed in the treatment of complicated urinary tract infections, intra-abdominal infections, hospital-acquired infections, and certain severe infections. Traditionally, an AUC_{24}/MIC target of at least 125 has been considered predictive of microbiological and clinical success against Gram-negative pathogens, while C_{max}/MIC $>$ 8–10 has also been proposed as an important complementary target, particularly for resistance suppression28–32. However, increasing evidence suggests that the conventional threshold of 125 may be insufficient in severe invasive infections. In patients with *Enterobacteriaceae* bloodstream infection, an AUC_{24}/MIC breakpoint of 250 was more strongly associated with

clinical cure than the traditional target, indicating that higher exposure may be required in bacteremia or other high-inoculum infections33.

On this basis, multiple studies have shown that standard ciprofloxacin dosing often fails to achieve these PK/PD targets in critically ill populations. In ICU patients, standard regimens such as 400 mg every 12 h frequently fail to attain adequate AUC_{24}/MIC when pathogen MICs approach 0.25–0.5 mg/L, and target attainment declines sharply as MIC increases30,33. In septic shock, profound pathophysiological changes and altered clearance further compromise exposure; even 400 mg every 8 h may provide satisfactory PTA only for isolates with MICs $\leq$ 0.25 mg/L, whereas higher doses such as 600 mg every 8 h may be needed for less susceptible pathogens, especially *P. aeruginosa*31. Similar concerns have been reported in patients receiving extracorporeal membrane oxygenation (ECMO), in whom ciprofloxacin pharmacokinetics remain highly variable and target attainment is strongly influenced by renal function and other physiological covariates34. Augmented renal clearance represents another major cause of underexposure, because it accelerates ciprofloxacin elimination and markedly reduces the likelihood of achieving effective AUC_{24}/MIC targets under conventional dosing32,34. Likewise, recent in vitro bladder and catheter-associated urinary tract infection models indicate that higher oral dosing, such as 750 mg every 12 h, may retain activity against *Escherichia coli* isolates with low-level resistance, whereas standard doses are mainly effective only for fully susceptible isolates35,36. Importantly, these studies consistently demonstrate that once MIC values rise above 0.25 mg/L, PTA decreases rapidly, and standard dosing becomes increasingly unreliable.

Levofloxacin

Levofloxacin is one of the most widely used respiratory fluoroquinolones in clinical practice. For common respiratory Gram-positive pathogens such as *S. pneumoniae*, an AUC_{24}/MIC $\geq$ 30 may be sufficient to achieve favorable microbiological efficacy; whereas for Gram-negative pathogens such as *Enterobacterales* and *Pseudomonas aeruginosa*, the conventional target value is AUC_{24}/MIC = 100–12537–40. In addition, resistance-suppression analyses suggested that MPC-based indices

Table 1
Pharmacokinetic characteristics of typical quinolone antibiotics.

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Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Levofloxacin	Approximately 99	6–8 h in healthy adults; significantly prolonged to 27 ± 10–35 ± 5 h in patients with renal impairment (creatinine clearance < 50 mL/min); extended to 76 ± 42 h in hemodialysis patients	24–38	Widely distributed in various tissues and body fluids throughout the body. Drug concentrations in most tissues and body fluids can reach or exceed the simultaneous plasma concentration. After a single oral dose of 500 mg, the drug concentration in lung tissue can reach 2–5 times the plasma concentration, ranging from 2.4 to 11.3 μg/g, and the concentration in bronchial mucosa is 9.4 ± 2.1	Mainly excreted via the kidneys, with approximately 87% of the administered dose excreted in urine as parent drug. Less than 4% is excreted in feces within 72 h, and < 5% is excreted in urine as desmethyl metabolites and N-oxide metabolites

Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Ciprofloxacin	70	4 h in healthy adult subjects; 8.7 ± 0.9 h in renal failure patients without hemodialysis; prolonged to 10.1 ± 1.2 h in patients receiving continuous ambulatory peritoneal dialysis	20–40	Widely distributed in various tissues and body fluids (including cerebrospinal fluid). Drug concentrations in tissues often exceed plasma concentrations, especially in renal tissues. Its cerebrospinal fluid concentration is usually less than 10% of the peak serum concentration, and drug levels in aqueous humor and vitreous humor are relatively low	Partially metabolized in the liver, and the metabolites still have weak activity. After oral administration, approximately 40%–50% is excreted via the kidneys as parent drug; about 15% as metabolites, and a portion is also excreted via bile and feces

Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Moxifloxacin	91	Approximately 12 h in healthy adult subjects. The half-life in critically ill patients with acute renal failure and patients with severe liver impairment (Child-Pugh Class C) is comparable to that in normal healthy subjects	30–50	Widely distributed in tissues and body fluids. Drug concentrations in bronchus, lung tissue, sinus tissue, muscle, skin blister fluid, saliva and intestinal fluid can be higher than or equal to the simultaneous plasma concentration. Moxifloxacin has good permeability to inflamed diabetic foot infected tissues. After oral and intravenous administration, the average concentrations in necrotic	Approximately 52% can be metabolized in the body to sulfides and glucuronides, accounting for 38% and 14% of the administered dose, respectively. Sulfides are mainly excreted via feces. Mainly excreted via the kidneys, with approximately 45% excreted as parent drug (about 20% in urine and 25% in feces)

Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Nemonoxacin	Approximately 106	Approximately 11 h in healthy adult subjects; no significant difference in patients with mild to moderate hepatic and renal impairment	16	Widely distributed in various human tissues and body fluids, with high concentrations in lung and skin and soft tissues	Undergoes minimal metabolism in humans. Mainly excreted via the kidneys, with approximately 70% excreted in urine as parent drug and about 6% excreted in feces as parent drug

Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Sitafloxacin	43–96	6.21 in healthy subjects; prolonged to 7.5–16.3 h in patients with renal impairment	46–55	Widely distributed in lung tissue, maxillary sinus mucosa, middle ear mucosa and tonsils, with a ratio to the average concentration of approximately 1.1–1.8	Mainly excreted via the kidneys as parent drug, with 80% of the drug excreted via the kidneys and 20% via feces

Drug	Oral Bioavailability (%)	$t_{1/2}$ (h)	Plasma Protein Binding (%)	Distribution	Metabolism and Excretion
Delafloxacin	Approximately 58.8	Approximately 8–9 h in healthy subjects; 8.9–14.9 h in patients with varying degrees of renal impairment. In end-stage renal disease patients after hemodialysis (creatinine clearance < 15 mL/min), the half-life can be prolonged to 15.0 ± 2.3 h	Approximately 84	Widely distributed with an apparent volume of distribution of 30.21–38.46 L, close to the volume of total body water	Glucuronidation is the main metabolic pathway. After a single intravenous injection, approximately 65% is excreted in urine as parent drug and glucuronide metabolites, and about 28% is excreted in feces as parent drug. After a single oral administration, 50% is excreted in urine as parent drug and glucuronide metabolites, and 48% is excreted in feces as parent

may better describe anti-mutant activity than MIC-based indices, with proposed thresholds such as $AUC_{24}/MPC > 25$ and $C_{max}/MPC > 2.2$ for restricting enrichment of levofloxacin-resistant *Staphylococcus aureus* subpopulations41.

For community-acquired respiratory tract infections caused by susceptible pathogens, oral 500 mg once daily may provide acceptable exposure in patients with preserved renal function, and a Chinese multicenter population PK/PD study supported this regimen as sufficient for major lower respiratory tract pathogens in that setting42. Nevertheless, several simulation studies have shown that 750 mg once daily provides more robust PK/PD target attainment than 500 mg once daily, particularly when pathogen MICs are elevated or when more consistent exposure is desired38–40. In healthy Chinese volunteers, MCS based on 750 mg intravenous dosing showed high cumulative fraction of response (CFR) values against *S. pneumoniae*, *H. influenzae*, *K. pneumoniae*, and MSSA, whereas activity against MRSA remained poor38. Similarly, population PK/PD modelling suggested that both 500 mg and 750 mg once daily may achieve favorable CFR against *S. pneumoniae*, but only 750 mg once daily approached optimal exposure against *Klebsiella spp*40. Additionally, in vitro studies show that a single high-dose administration (e.g., 1000 mg or 750 mg daily) is more effective than divided doses (e.g., 500 mg every 12 h).

Levofloxacin clearance in elderly patients is heavily influenced by creatinine clearance, requiring dosage adjustments to meet the AUC_{24}/MIC target. A study found creatinine clearance to be the sole factor affecting clearance, with an $AUC_{24}/MIC \geq 95.7$ predicting better outcomes. Simulations showed over 80% target attainment for *E. coli* and *H. influenzae*, but only borderline or insufficient levels for *Staphylococcus aureus* and *P. aeruginosa*43. In the context of ventilator-associated pneumonia in intensive care unit settings, patients frequently exhibit an increased apparent volume of distribution and augmented renal clearance. To effectively target non-fermenting bacteria with a MIC near the clinical breakpoint, it is necessary to increase the dosage to 1000 mg/day (e.g., 500 mg every 12 h) to achieve the optimal target of $AUC_{24}/MIC \geq 100$–125. For deep-seated infections such as bone and joint infections, levofloxacin demonstrates excellent tissue penetration, with a tissue-to-plasma concentration ratio ranging from 1.9 to 2.344. For infections caused by *S. aureus* or Enterobacterales, a dosing regimen of 500–750 mg every 24 h is recommended. However, in cases involving refractory pathogens such as *P. aeruginosa*, a regimen of 500 mg every 12 h is advised.

Moxifloxacin

Moxifloxacin is a fourth-generation fluoroquinolone. Compared to levofloxacin, moxifloxacin exhibits more potent activity against *S. pneumoniae*, certain Gram-positive bacteria, atypical pathogens, and anaerobes, thereby occupying a crucial role in the management of community-acquired respiratory tract infections. Furthermore, moxifloxacin is primarily metabolized by the liver and eliminated via non-renal pathways, meaning that renal function has a minimal impact on its

systemic exposure. This pharmacokinetic characteristic provides considerable dosing convenience for patients with renal impairment.

For common respiratory pathogens, MCS-based analyses have shown that the standard regimen of moxifloxacin 400 mg once daily generally provides adequate target attainment. In the study by Yamagishi et al., the PK/PD breakpoint of moxifloxacin 400 mg once daily was 0.5 μg/mL for *S. pneumoniae* at the target AUC/MIC $\geq$ 30, and 0.125 mg/L for *H. influenzae* and *Moraxella catarrhalis* at the target AUC/MIC $\geq$ 100; notably, the PTA for hypothetical community-acquired pneumonia reached 100%, indicating that the conventional 400 mg once-daily regimen is generally sufficient for susceptible respiratory isolates45. Likewise, in the POET substudy on oral step-down treatment for infective endocarditis, oral moxifloxacin 400 mg once daily, evaluated against the PK/PD target AUC_{24}/MIC $>$ 30, achieved relatively favorable PTA values, particularly when pathogen-specific MICs rather than clinical breakpoints were used, supporting its potential role in selected high-burden infections23.

In multidrug-resistant tuberculosis (MDR-TB), the exposure targets required for maximal mycobacterial killing and resistance suppression are substantially higher than those used for routine bacterial infections. In Ethiopian patients with MDR-TB, Sidamo et al. demonstrated that for moxifloxacin, the PTA for the maximal kill target AUC_{24}/MIC $\geq$ 53 at a critical MIC of 0.25 mg/L was approximately 94.4% even at 600 mg, whereas the PTA for the resistance suppression target AUC_{24}/MIC $\geq$ 100 increased from only 50% at 600 mg to 77.8% at 800 mg and 94.4% at 1000 mg, indicating that standard dosing may be insufficient when resistance prevention is a major therapeutic objective46. Similar findings were reported in Chinese patients with MDR-TB and type II diabetes mellitus, in whom glycated hemoglobin significantly influenced both clearance and volume of distribution of moxifloxacin. In that study, the WHO-recommended dose of 400 mg once daily achieved PTA $>$ 90% only when MICs were $\leq$ 0.25 mg/L, whereas doses of 600–800 mg/day were needed to maintain adequate PTA at an MIC of 0.5 mg/L47.

Host physiological alterations may also substantially affect moxifloxacin exposure and thereby necessitate individualized dosing. In post-bariatric surgery patients, Colin et al. found that moxifloxacin pharmacokinetics were best described by a three-compartment model, with lean body mass identified as an important predictor of clearance48. Their PK/PD simulations showed that although a standard 400 mg dose could remain acceptable for bacterial eradication at lower MICs, attainment of more stringent targets, especially those associated with suppression of resistance emergence, was markedly reduced in patients with higher lean body mass; indeed, when the MIC reached 0.5 mg/L, the PTA for eradication approached zero in patients with high lean body mass.

Nemonoxacin

Nemonoxacin is a novel non-fluorinated quinolone. In vitro and in vivo studies consistently support AUC_{24}/MIC as the principal PK/PD index for *S. pneumoniae*, with targets of 47.05 for a 3-log10 reduction in an in vitro infection model and 44.4 for a 2-log10 kill in a neutropenic murine lung infection model49,50. In addition, an integrative population PK/PD analysis in Chinese CAP patients identified pathogen-specific clinical targets, including AUC_{24}/MIC values of 63.3, 97.8, and 115.7 for *S. pneumoniae*, *S. aureus*, and *H. influenzae*, respectively, whereas $\%T >$ MIC appeared more predictive for *K. pneumoniae* (target 7.96%)17. These data indicate that nemonoxacin PK/PD target attainment is largely pathogen dependent and should not be interpreted using a single universal threshold.

In routine CAP management, oral nemonoxacin 500 mg once daily is generally adequate and has demonstrated clinical efficacy non-inferior to levofloxacin in phase 3 trials51, with meta-analytic evidence also supporting comparable overall efficacy and tolerability52. Population PK/PD simulations further showed that this regimen achieved PK/PD cutoff values above the MIC_{90} for *S. pneumoniae* and *S. aureus*, with CFR $>$ 93%17. Nevertheless, target attainment becomes less reliable in selected scenarios. In particular, 500 mg every 24 h may be suboptimal for pathogens with higher MICs or for *H. parainfluenzae*, for which 750 mg every 24 h provided better CFR than the standard regimen17. Similarly, murine PK/PD analysis suggested that 750 mg every 24 h was required to achieve 90% PTA at MIC = 1 mg/L against *S. pneumoniae*, whereas 500 mg every 24 h was more appropriate for isolates with MIC $\leq$ 0.5 mg/L. Thus, standard dosing remains suitable for highly susceptible pathogens but may require intensification when MIC values increase toward the upper susceptible range.

By contrast, dose optimization in severe renal impairment aims to avoid overexposure rather than underexposure. Because nemonoxacin is predominantly renally eliminated, creatinine clearance is a major determinant of its clearance. In patients with severe renal impairment,

500 mg every 24 h results in approximately two-fold higher exposure than in subjects with normal renal function, while MCS supports 500 mg every 48 h as the most appropriate adjusted regimen, maintaining PTA of 92.7% and CFR $>$ 99% at MIC $\leq$ 1 mg/L53. Importantly, simple dose reduction to 250 mg every 24 h appears inadequate for higher-MIC isolates. Site-specific considerations are also relevant: in acute lower urinary tract infection, 500 mg every 24 h showed acceptable efficacy in a prospective multicenter study54, whereas in difficult MRSA infections with elevated vancomycin MIC, nemonoxacin may be more useful as a combination partner with vancomycin than as an empirically escalated monotherapy55. Overall, nemonoxacin dosing should be individualized according to pathogen MIC, infection syndrome, and renal function, with 500 mg q24h as the standard regimen for susceptible CAP, 750 mg every 24 h considered when higher exposure is required, and 500 mg every 48 h recommended

in severe renal impairment.

Sitafloxacin

A population PK/PD study in patients with community-acquired respiratory tract infections showed that bacterial eradication rates approached 96% when $AUC_{24}/MIC \geq 30$ or $C_{max}/MIC \geq 2$, suggesting that $AUC_{24}/MIC \geq 30$ is an important clinical PK/PD target for sitafloxacin56. Subsequent studies based on population pharmacokinetic modeling and MCS further indicated that, under commonly used dosing regimens, the PK/PD cut-off of sitafloxacin against common respiratory pathogens is approximately 0.06–0.125 mg/L, although target attainment varies substantially across pathogens and dosing regimens57–60.

The PK/PD characteristics of sitafloxacin are markedly infection-site dependent. In critically ill patients with pneumonia, sitafloxacin achieves relatively favorable exposure in epithelial lining fluid (ELF); however, delayed absorption, increased clearance variability, and substantial inter-individual variation may compromise target attainment. Under the standard regimen of 100 mg every 12 h, satisfactory PTA and CFR are mainly achieved for low-MIC isolates, whereas target attainment declines significantly as MIC increases, particularly in ELF. In urinary tract infection models, the antibacterial effect of sitafloxacin is more closely associated with $UAUC_{24}/MIC$, and the targets required to achieve a 2-log10 bacterial reduction range from 99.45 to 128.95 for different multidrug-resistant pathogens, indicating that urinary exposure rather than plasma exposure should be preferentially considered in this setting59. Moreover, simulation studies in multidrug-resistant or carbapenem-resistant *A. baumannii* showed that recommended sitafloxacin monotherapy regimens generally fail to achieve optimal PK/PD targets, whereas combination with colistin can markedly improve PTA and CFR by reducing the effective MIC60.

Delafloxacin

In the study by Lepak and Andes, the median $fAUC_{24}/MIC$ required for 1-log10 bacterial killing was 7.92 against *S. aureus*, 3.36 against *S. pneumoniae*, and 55.2 against *K. pneumoniae*, whereas the corresponding stasis targets were 1.42, 0.56, and 40.3, respectively61. Another murine lung model reported somewhat different but directionally consistent results, with median $fAUC_{24}/MIC$ values associated with 1-log10 kill of 24.7 for MRSA, 31.8 for *S. pneumoniae*, and 9.6 for *K. pneumoniae*, again supporting $fAUC_{24}/MIC$ as the principal PK/PD index of efficacy for delafloxacin62.

The PK/PD behavior of delafloxacin also appears to be influenced by tissue penetration and host-related factors. In murine lung infection studies, delafloxacin achieved favorable intrapulmonary exposure, with epithelial lining fluid concentrations exceeding free plasma concentrations, supporting its potential utility in lower respiratory tract infections63. Population pharmacokinetic analyses further showed that delafloxacin is adequately described by a three-compartment

model with mixed linear and nonlinear clearance, with body weight identified as an important covariate affecting exposure64. MCS based on this model indicated that, in patients with ABSSSIs caused by MRSA, the standard regimen of 300 mg intravenously every 12 h was associated with a PTA $>$ 90% at an MIC of 0.25 mg/L, whereas a reduced regimen of 200 mg every 12 h might still achieve adequate target attainment in patients weighing $<$ 60 kg. In addition, previous population PK analyses integrating phase I data supported exposure equivalence between 300 mg intravenously and 450 mg orally, which provides a pharmacological basis for IV-to-oral switch therapy18,63.

Conclusions and perspectives

Quinolones, as a typical class of concentration-dependent antimicrobial agents, exhibit clinical efficacy and resistance-suppression effects that are closely associated with in vivo drug exposure. PK/PD-based individualized dose optimization is therefore an important strategy for improving the clinical efficacy of quinolones and controlling the emergence of resistance.

Although significant progress has been made in the PK/PD research of quinolones, several limitations remain. First, some PK/PD target values are still primarily derived from in vitro or animal infection models, lacking adequate validation from large-sample clinical outcomes. Second, the pathogen stratification, target thresholds, and endpoint definitions adopted across different studies are not entirely consistent, which limits the cross-sectional comparison and standardized application of the results. Third, real-world pharmacokinetic data remain relatively scarce for special populations, such as critically ill patients, those with augmented renal clearance, patients on ECMO, obese individuals, and those receiving organ function support. Furthermore, the accumulation of clinical evidence for novel quinolones is still limited, and their long-term resistance evolution trends and optimal dosing strategies require further investigation.

In conclusion, PK/PD theory has become a core tool for the rational use and dose optimization of quinolones. Future clinical practices should further transition from traditional empirical prescribing to a precision and individualized treatment paradigm based on pathogen MICs, host characteristics, and drug exposure. This shift aims to maximize efficacy while minimizing the emergence of resistance, thereby promoting the long-term rational clinical application of quinolone antibiotics.

Declarations

Not applicable.

CRediT authorship contribution statement

Siwei Guo: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Miaomei Tian:** Data curation, Investigation, Validation, Writing - original draft. **Jingji Dai:** Formal analysis, Resources, Visualization, Writing - review & editing. **Xin Li:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing - review & editing.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have read and agreed to the published version of the manuscript and give their consent for publication in this journal.

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Authors' other information

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