An Insight about Quinolone Resistance

Safia Salama Shaban, Ayman A Allam, Wafaa Salah Abdelhaleem Metwally, Zeinab Saed Mohamed Ibrahim
Medical Microbiology and Immunology Department, Faculty of Medicine - Zagazig University, Egypt
Corresponding author: Safia Salama Shaban
E-mail: saelghoneimy@gmail.com, sselghonimy@medicine.zu.edu.eg
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Abstract

Quinolone resistance in bacteria represents a significant global health threat, compromising the efficacy of crucial antibiotics used to treat a wide range of infections. This resistance arises primarily through mutations in genes encoding topoisomerases, the enzymes targeted by quinolones. These mutations, often located in the quinolone resistance-determining regions (QRDRs) of *gyrA*, *gyrB*, *parC*, and *parE*, reduce drug binding affinity and consequently inhibit enzymatic inhibition. However, resistance is a multifaceted phenomenon extending beyond target site mutations. Efflux pumps, integral membrane proteins that actively expel antibiotics from the bacterial cell, play a crucial role in quinolone resistance. Overexpression or increased activity of these pumps, often driven by mutations in regulatory genes or by the presence of efflux pump-modifying genes on mobile genetic elements, effectively reduces intracellular drug concentrations, diminishing the efficacy of quinolones. Furthermore, the impermeability of the outer membrane in Gram-negative bacteria serves as a significant barrier to quinolone entry, contributing to resistance. Mutations affecting porin proteins, which form channels in the outer membrane, further restrict antibiotic penetration. The acquisition of resistance genes via horizontal gene transfer, particularly through plasmids and transposons, adds another layer of complexity. These mobile genetic elements can carry genes encoding enzymes that modify or inactivate quinolones, effectively neutralizing their antibacterial activity. The dissemination of such resistance genes across diverse bacterial species contributes to the widespread emergence and persistence of quinolone resistance. Understanding the complex interplay between target site mutations, efflux pump activity, membrane permeability, and horizontal gene transfer is crucial for developing effective strategies to combat quinolone resistance. These strategies include developing new quinolone derivatives that circumvent resistance mechanisms, optimizing antibiotic stewardship programs to minimize the selective pressure for resistance, and exploring alternative therapeutic approaches such as combination therapies and novel antimicrobial agents. Ultimately, a multi-pronged approach involving surveillance, prevention, and development of new treatment options is essential to mitigate the escalating threat posed by quinolone resistance.

Keywords: Quinolone resistance

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Introduction

Quinolones are synthetic antibiotics used to treat Gram-negative bacterial infections, although modifications have extended their use to Gram-positive infections. They inhibit nucleic acid synthesis by targeting bacterial DNA gyrase and topoisomerase IV, preventing DNA synthesis and leading to cell death. In Gram-negative bacteria, gyrase is the primary target, while topoisomerase IV is the preferential target in Gram-positive bacteria. [1]

DNA gyrase comprises GyrA and GyrB subunits, while topoisomerase IV consists of ParC and ParE subunits. These enzymes create staggered DNA cuts, forming enzyme-DNA complexes before breaking and rejoining the DNA. Fluoroquinolones bind to the helix-4 of GyrA or ParC subunits, forming a drug-enzyme-DNA complex that prevents DNA re-ligation. This mechanism classifies quinolones as "topoisomerase poisons". [2]

Comparison of the clinically relevant features of novel fluoroquinolones.

Novel Fluoroquinolons	**Delafloxacin**	**Finafloxacin**	**Zabofloxacin**
Chemical structure	Unique anionic (non-zwitterionic) structure, with special substituents and augmented polarity.	Zwitterionic chemical structure of fluoroquinolones supplemented with substituents.	Zwitterionic chemical structure of fluoroquinolones supplemented with substituents (two forms are available).
Bioavailability	58.8%	75% (by oral use)	No data available.
Protein binding	Approximately 84%	No data available.	No data available.
Mechanism of action	Dual-targeting of DNA gyrase and topoisomerase IV enzymes of gram-positives and gram-negatives with equal affinity. Increased bactericidal effect in acidic pH	Dual-targeting (weaker effect compared to other group members) of DNA gyrase and topoisomerase IV enzymes of gram-positives and gram-negatives with equal	Dual-targeting of DNA gyrase and topoisomerase IV enzymes, predominantly of community-acquired respiratory tract pathogen gram-

Novel Fluoroquinolons	Delafloxacin	Finafloxacin	Zabofloxacin
		affinity. Increased bactericidal effect in acidic pH.	positives, and some gram-negatives. Ineffective against major nosocomial gram-negatives.
Approved Indication	Acute bacterial skin and skin-structure infections (ABSSSI) of adults caused by MRSA, MSSA, *S.haemolyticus*, *S. lugdunensis*, *S. agalactiae*, *Streptococcus anginosus Group*, *S. pyogenes*, *E. faecalis*, *E. coli*, *E. cloacae*, *K.pneumoniae*, and *P.aeruginosa*. Community-Acquired Bacterial Pneumonia of adults caused by *S.pneumoniae*, MSSA, *K. pneumoniae*, *P.aeruginosa*, *H. influenzae*, *H. parainfluenzae*, *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*.	Otic suspension for acute otitis externa caused by *P. aeruginosa* and *S. aureus* in patients age one year and older.	Oral administration for acute bacterial exacerbation of chronic obstructive pulmonary disease (COPD).

Quinolones halt DNA replication within minutes of addition to bacterial cultures. The drug concentration preventing DNA replication correlates with the minimum inhibitory concentration (MIC), and DNA synthesis resumes after drug removal. [3]

Quinolones are categorized into generations (first, second, third, fourth) based on their discovery and antibacterial properties. First- and second-generation effects are linked to reactive oxygen species (ROS) production; however, the killing action of norfloxacin does not always correlate with cell death at high ROS concentrations. [4]

Nalidixic acid, the first quinolone, was discovered as an impurity in chloroquine synthesis in 1962. It showed moderate activity against Gram-negative bacteria (except *Pseudomonas aeruginosa*) and was used to treat uncomplicated urinary tract infections. However, limitations included low potency, high protein binding, short half-life, and poor bioavailability. Subsequent compounds demonstrated improved potency, broader spectra, better pharmacokinetics, and reduced resistance development. [51]

Fluoroquinolones, a quinolone subgroup, feature nitrogen at position 8 and fluorine at position 6 of their naphthyridine nucleus. Norfloxacin, introduced in 1986, had limited success due to low blood/fluid concentrations and Gram-positive activity. Flumequine, the first fluoroquinolone, was abandoned due to ocular toxicity. [6]

The addition of a piperazine ring to C-7, along with the C-6 fluorine, created second-generation quinolones with broader activity, better bioavailability, improved pharmacokinetics, reduced toxicity, and decreased susceptibility to single-point mutations leading to resistance. [7]

Third-generation fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin) offer benefits such as activity against *Streptococcus* spp., *K. pneumoniae*, and other Enterobacteriaceae, along with high tissue penetration and half-life. Ciprofloxacin exhibits improved efficacy and reduced toxicity compared to earlier generations, possibly due to enhanced chromosome fragmentation. Gatifloxacin is used topically due to severe side effects (hypoglycemia). Fourth-generation FQs (moxifloxacin) target anaerobic bacteria and are used in multidrug-resistant tuberculosis treatment. [8]

Ciprofloxacin (1987) is a landmark second-generation quinolone with effective systemic activity, excellent tissue distribution, and activity against Gram-positive bacteria. Ofloxacin, with similar characteristics, is on the WHO list of essential medicines. Ciprofloxacin is a first-line treatment for low-risk febrile neutropenia in cancer patients and a second-line treatment for cholera. It is also effective against Enterobacteriaceae-induced osteomyelitis, prostatitis, and septicemia. Levofloxacin (an ofloxacin stereoisomer) and moxifloxacin treat multidrug-resistant infections. Many newer fluoroquinolones have been withdrawn due to safety concerns. [9]

Table Classification of fluoroquinolones according to classes

I	Oral fluoroquinolones with indications essentially limited to urinary tract infections (in Germany)	Norfloxacin Pefloxacin
II	Fluoroquinolones with broad indications for systemic use	Enoxacin Fleroxacin Ofloxacin Ciprofloxacin
III	Fluoroquinolones of improved activity against Gram-positive and 'atypical' pathogens	Levofloxacin Sparfloxacin Grepafloxacin
IV	Fluoroquinolones with improved activity against Gram-positive and 'atypical' pathogens as well as anaerobes	Gatifloxacina Trovafloxacin Moxifloxacina Clinafloxacina

Early quinolones (ciprofloxacin, ofloxacin) had limited activity against Gram-positive bacteria, primarily *Propionibacterium acnes* and some *Clostridium perfringens* strains. Clinafloxacin showed strong activity against anaerobes but was not approved due to phototoxicity and hypoglycemia. [10]

Newer fluoroquinolones (delafloxacin, finafloxacin, zabofloxacin) possess favorable properties: broad antibacterial spectra, good tissue penetration, and fewer adverse effects. Delafloxacin, an anionic fluoroquinolone, targets Gram-positive and Gram-negative bacterial DNA gyrase and topoisomerase IV. Its anionic nature enhances activity in acidic environments (phagolysosomes, biofilms, abscesses). It is approved for ABSSSI and CABP and shows promise against fluoroquinolone-resistant *P. aeruginosa* lung infections. Besifloxacin and finafloxacin are topical FQs. [11]

Nemonoxacin, a non-fluorinated FQ, exhibits activity against Gram-negative and Gram-positive bacteria, including MRSA and quinolone-resistant *C. difficile*. It is also effective against *Helicobacter pylori* and vancomycin-resistant pathogens. [12]

Quinolones have been explored for prophylactic treatment in various patient populations and for certain parasitic, fungal, and viral infections. However, increasing resistance limits these applications. The FDA and EMA recommend against first-line use due to resistance and adverse effects (tendon rupture, aortic aneurysm/dissection). Quinolones remain approved for various infections, including gastrointestinal and lower respiratory tract infections, anthrax, plague, salmonellosis, skin, bone, and

joint infections, prostatitis, typhoid fever, and some sexually transmitted infections. The WHO recommends them as second-line treatment for multidrug-resistant tuberculosis. [13]

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