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Review Article

Resistance Mechanisms in Various Bacteria Against DNA Gyrase Inhibitors: A Concise Review

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Abstract

DNA gyrase, a bacterial type 2 isomerase is a critical enzyme to maintain DNA supercoiling during replication and transcription. DNA gyrase inhibitors have been widely used to treat serious infections, bearing great importance in clinical settings. Multiple inhibitors, including fluoroquinolones (FQs) and other gyrase inhibitors stabilizes the DNA-enzyme cleavage complex and halt DNA re-ligation. The widespread use of these inhibitors in the form of antibiotics introduces antimicrobial resistance (AMR). Emerging evidence indicates that resistance to DNA gyrase inhibitors is driven by a dynamic interplay of genetic mutations, adaptive cellular responses, and mobile genetic elements (MGEs). Across Gram-negative and Gram-positive pathogens, as well as in acid-fast bacteria, distinct yet overlapping molecular strategies have evolved to reduce drug susceptibility and promote survival under antimicrobial pressure. These bacterial species are adapted to act mechanistically, hence becoming resistant to the antibiotics. This review explores the molecular basis of resistance to DNA gyrase inhibitors in clinically significant bacterial pathogens, highlighting how evolutionary adaptation and selective pressure continue to reshape the landscape of antibacterial therapy. Understanding these processes is crucial for informing future treatment strategies and mitigating the growing threat of resistant infections.

Keywords: DNA gyrase, Antimicrobial resistance, Efflux pump, Plasmid-mediated resistance, Multidrug resistance

1. Introduction

DNA supercoiling is a topological molecular mechanism that compensates for topological changes applied to the double helical structure of DNA. Bacterial DNA is generally underwound, containing more base pairs per turn than supercoiled DNA. During molecular processes, the movement of replication machinery introduces positive supercoiling ahead of the DNA polymerase enzyme (Junier et al. 2023). DNA gyrase, a type 2 bacterial topoisomerase that acts as a protein complex with four subunits, maintains the genomic organization of bacteria by preventing DNA from getting supercoiled through an appropriate level of negative supercoiling within the cell (Joshi and Osheroff 2025). The structure of DNA gyrase involves two highly conserved sub-units, DNA gyrase subunit A (GyrA) and DNA gyrase subunit B (GyrB). These sub-units are a part of the working mechanism of DNA topology conservation and avert superfluous torsional strain. The highly flexible nature of the enzyme facilitates mechanistic roles by adopting multiple conformations. A quaternary structure of 370 kDa molecular mass is structurally stabilized by three molecular interfaces called as DNA-gate, N-gate,

and C-gate, which contribute to the multi-domain organization of the enzyme (Vanden Broeck et al. 2019).

Gyrase inhibitors, a class of potent antibiotics, treat bacterial infections by targeting bacterial DNA gyrase and topoisomerase 4 such as in the case of fluoroquinolones (FQs). The effectiveness of FQs are evident as they retain their mechanistic action against persistent infections, where non-dividing and metabolically inactive cells are present. The broad-spectrum antimicrobial activity is contributed through the dual targeting nature, where topoisomerase 4 is targeted predominantly in Gram-positive bacteria and DNA gyrase primarily in Gram-negative bacteria (Geremia et al. 2024). Their antibacterial action, combined with pharmacokinetic parameters, maximizes their effectiveness. Ciprofloxacin, the second-generation FQ, has around 90% oral availability. FQs have high tissue penetration, with peak plasma concentrations being attained within two hours of dosing. The extensive tissue dispersion increases effectiveness, demonstrating its importance in treating infections such as otitis externa (Wahood et al. 2025). However, despite their clinical benefits, FQs resistance has emerged as a major global health challenge, largely due to widespread antibiotic use since the mid-1990s. Presently, Asian and European countries exhibit the greatest rates (27%), whereas the United States has a lower prevalence (8%). Ciprofloxacin-resistant uropathogenic *Escherichia coli (E. coli)* (UPEC) is more common in India with more than 60% of cases and similar trends surface in Turkey and China. This global issue has a significant mortality rate, with over 0.7 million fatalities worldwide each year, highlighting the critical need for antimicrobial stewardship, local resistance monitoring, and alternative therapeutic methods (Ruiz-Lievano et al. 2024).

The objective of this review is to summarize and analyze the mechanisms by which bacteria develop resistance to DNA gyrase inhibitors. It focuses on the genetic, biochemical, and cellular changes that reduce drug effectiveness, including target gene mutations, efflux pump overexpression, plasmid-mediated protection, and other adaptive strategies. By examining key bacterial species, the review aims to provide a clear understanding of how resistance arises at the molecular level and to highlight its implications for the treatment of bacterial infections.

2. Mechanism of Action of DNA Gyrase Inhibitors

The mechanistic action of DNA Gyrase involves enzymatic action. It starts by binding with DNA-gate through "G-segment", where it causes cleavage of both DNA strands, leading to transportation of second T-segment through the break. These coordinated steps are facilitated by conformational changes with the expenditure of energy. A subunit wind DNA through its C-terminal domain (CTD). This introduces negative supercoiling into bacterial DNA and reduces torsional stress, which is critical for DNA topology maintenance. Any disruption in the following mechanism causes uncontrolled division of bacteria through the impairment of negative supercoiling. DNA gyrase inhibitors work to counteract the pathogenic effects by controlling enzymatic actions. This class includes compounds such as aminocoumarins, FQs, spiropyrimidinetriones (SPTs), and novel bacterial topoisomerase inhibitors (NBTIs). The effectiveness of these drugs are evident, where they are found to halt replication and transcription of bacterial species (Fukuda et al. 2026). DNA gyrase inhibitors such as FQs intervenes in cleavage process, where they bind non-covalently to the active site of the gyrase heterotetramer and interpose between bases of DNA at the cleavage site. **Figure 1** illustrates the mechanistic action of DNA gyrase inhibitor, FQ (ciprofloxacin). The binding mechanism is mediated through non-covalent interactions to stabilize cleaved DNA and prevent its re-ligation. Non-covalent interactions include non-catalytic chelation with Mg^{2+}, where chemical groups (C-3/C-4 keto group) attached to the 3rd and 4th carbon of quinolone ring via water

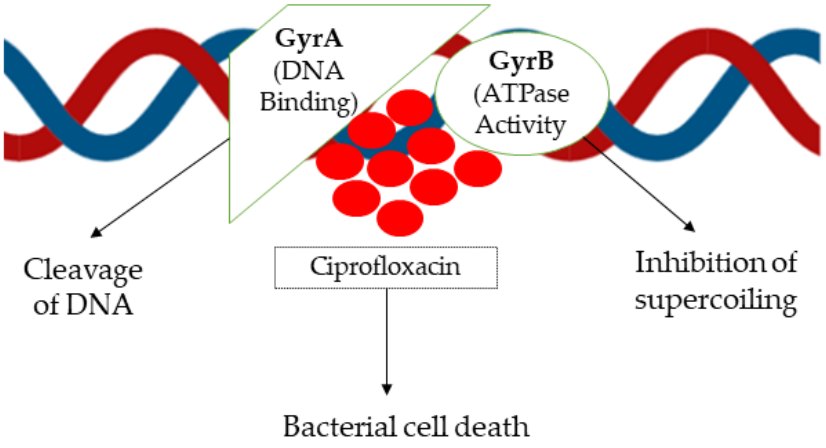

Figure 1: Overview of DNA Gyrase Inhibitor Mechanistic Action.

bridge, forming hydrogen bonds with GyrA residues Asp87 and Ser83 (Spencer and Panda 2023). These interactions with the following mechanisms manage the supercoiling of DNA. The other class of gyrase inhibitor, aminocoumarins, work in a different manner, where their mechanistic action involves interaction towards N-terminal domain of GyrB through tight binding to the ATP-binding pocket, where they compete with the ATP and blocks its binding. This disrupts mechanistic effect of generation of ATP targeting mitochondrial and cellular activity. Inhibition of this ATP-driven energy transduction prevents DNA supercoiling, leading to a loss of negative supercoils and relaxation of DNA, which disrupts replication and transcription (Anderle et al. 2008). The effectiveness of aminocoumarins is comparable to that of FQs. Biochemical studies suggest that aminocoumarins act as potent DNA gyrase inhibitors, and their activity can be further enhanced when modulated by environmental factors, such as potassium glutamate (K-Glu), where it enhances the sensitivity of *E. coli* DNA gyrase to aminocoumarin antibiotics, indicating that ionic conditions can modulate enzyme-drug interactions (Alt et al. 2011). SPTs target DNA gyrase by linking to a specific pocket within the cleavage complex, and interacts with GyrB residues. Its process does not require Mg^{2+} ions to stabilize the DNA-enzyme complex and lacks the standard quinolone binding mechanism, hence reducing the quinolone resistant determinants effects. (Bradford et al. 2020). NBTIs binding mechanism to a cleavage complex is same as SPTs except that NBTIs interacts with GyrA residues. The binding site of NBTIs is distinct from the places of FQ-resistance mutations on DNA gyrase; therefore, they are effective against bacteria resistant to FQs (Kolaric, Anderluh, and Minovski 2020). The interactions of NBTIs involve hydrophobic interaction with the binding pocket between two GyrA subunits, through which it interacts with conserved residues. The stabilized DNA-gyrase cleavage complex is facilitated by intrinsic flexibility of the binding pocket, promoting optimal binding and enhancing the potency of NBTIs (Franco-Ulloa et al. 2018).

3. Resistance Mechanisms

In this section, bacterial resistance mechanisms towards DNA gyrase inhibitors are discussed in detail. The mechanisms involve target site mutations, efflux pump overexpression, plasmid-mediated resistance, and other mechanistic factors such as biofilm formation and compromised permeability.

Among all, mechanism of mutations of GyrA and GyrB in the quinolone resistance-determining regions (QRDRs) is the common one, where amino

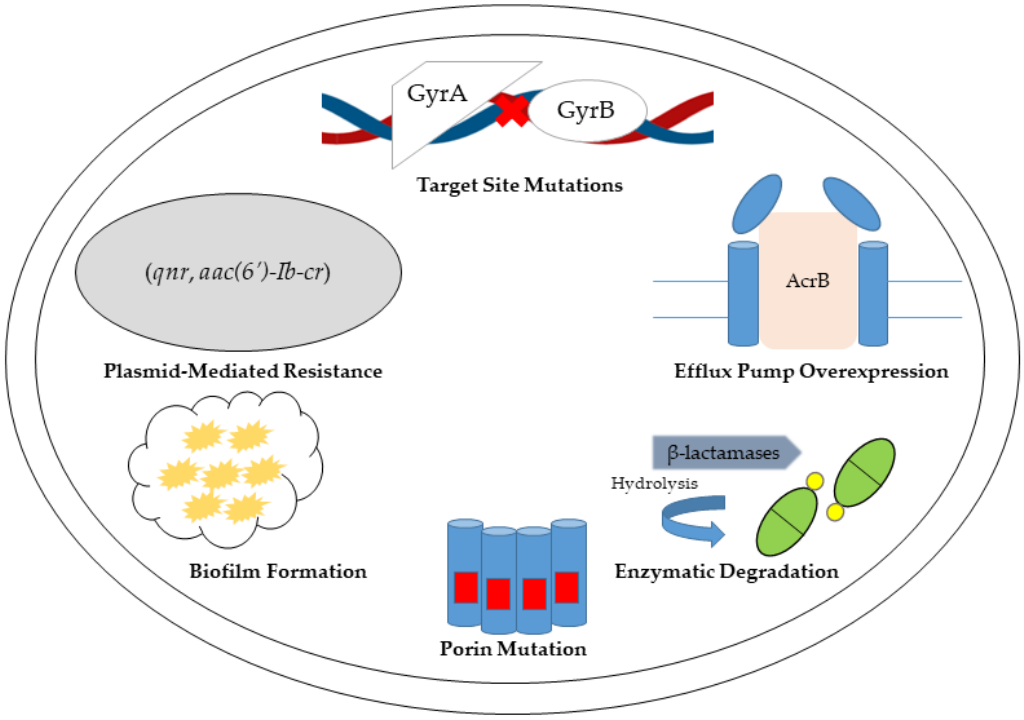

Figure 2: Resistance Mechanisms in Bacterial Cell.

acid changes occur, causing poor inhibitor binding. This allows DNA replication, leading to bacterial growth and persistent of infections. The evidence of target-site mediated resistance is the Ser83 substitution in QRDR of *gyrA* gene in *E. coli* shows high-level resistance to FQs. The substitution of serine at position 83 with tryptophan (Ser83Trp) or leucine (Ser83Leu) causes high-level FQ resistance. The catalytic activity of DNA gyrase continues which increases the survival chances of bacteria under the drug pressure. Ser83Trp residue alteration also modify drug sensitivity profiles towards other inhibitors, underscoring the critical role of this residue in determining inhibitor binding specificity (Gruger et al. 2004).

Other than mutation effects, mechanisms of resistance, overexpression of multidrug efflux pumps is evident. Overexpression of multidrug efflux pumps represents a significant mechanism of resistance to DNA gyrase inhibitors, particularly in Gram-negative bacteria. These pumps acts as protein transport systems that actively removes excessive amount of antibiotics from the bacterial cell. In *E. coli*, the AcrAB-TolC efflux pump system, consisting of AcrA (Acridine resistance protein A), AcrB (Acridine resistance protein B), and TolC (outer membrane channel TolC) is a member of resistance-nodulation-division (RND) family of transporters, plays a major role in reducing intracellular FQ levels and decreasing drug effectiveness. Mutations in regulatory genes are responsible for overproduction of pump (Smith, Fernando, and King 2024). In clinical settings, bacterial growth mechanisms are dependent upon drug dosage, where higher drug doses stop bacterial growth. Experimental studies on overexpression of AcrAB-TolC efflux pump proteins, particularly AcrA and AcrB is associated with increased minimum inhibitory concentration (MIC) values. Conversely, deletion of *acrA* or *acrB* genes results in greater intracellular accumulation of antibiotics and restoration of susceptibility. As AcrAB–TolC system expel multiple classes of antibiotics, its overexpression also contributes to multidrug resistance (MDR) (Kherroubi, Bacon, and Rahman 2024). The following efflux system causes

Table 1: Resistance in Various Bacterial Species.

Bacterium	Gene/Target	Resistance Mechanisms	Clinical Relevance	References
E. coli	*gyrA*, *qnr*, AcrAB-TolC, *aac(6')-Ib-cr*	QRDR target-site mutation, Efflux pump overexpression	UTI treatment failure	(Tewawong et al. 2025)
P. aeruginosa	*gyrA*	Reduced permeability	MDR phenotype	(Milojkovic et al. 2020)
S. pneumonia	parC, parE	Topoisomerase 4 mutation	Respiratory infections	(Collins and Osheroff 2024)
S. aureus	*gyrA*, *parC*	Target-site modification	Skin infections	(Brdova, Ruml, and Viktorova 2024)
M. tuberculosis	*gyrA*	QRDR mutation	Indicator of FQ-resistant TB	(Tu et al. 2025)

resistance by pulling out drugs from bacterial cells, however, resistance can also plasmid-mediated mechanisms through horizontal transfer. The horizontal transfer followed by plasmid-mediated determinants, two genes *qnr* (encoding pentapeptide repeat proteins that protect gyrase) and *aac(6')-Ib-cr* (aminoglycoside acetyltransferase modifying quinolones) mediates resistance mechanisms, where *qnr* gene encodes for repeating sequence of five amino acids. The protein blocks the effect of quinolones. This partially protects the DNA gyrase and causes low-level resistance. Likewise, the modified version of aminoglycoside acetyl transferase with variant can act on quinolones particularly ciprofloxacin as AAC(6')-Ib-cr works through specific substrate binding. Binding causes modification of antibiotics and reduces its efficacy (Jacoby, Strahilevitz, and Hooper 2014). Both genes conferring low-level resistance, if co-exist with other mutations such as chromosomal mutation or dysregulated efflux systems can further facilitate the resistance at high level, where quinolone-resistant mutants cause increase in AMR (Kareem et al. 2021). Beyond these mechanisms, bacteria acquire resistance through other mechanisms, where membrane permeability differences, modification or degradation of antibiotic enzymes, and bacterial biofilm production can also contribute to MDR phenotypes. Synergistic effect of these mechanisms with intrinsic and acquired resistance strategies further complicates the treatments in clinical settings (Elshobary et al. 2025). Mutations in porin proteins, such as OprD cause high-level resistance, where uptake of antibiotics such as carbapenems is reduced. Changes due to mutations are not limited to OprD; modifications in OprB, OprE, OprP, and OprO also participate in the alteration of membrane permeability, due to which hydrophilic antibiotics cannot enter. β-lactamases and metallo-β-lactamases (MBLs) enzymes inactivate antibiotic function. These enzymes are produced by *Pseudomonas aeruginosa* (*P. aeruginosa*), where β-lactamases hydrolyze β-lactam antibiotics, while aminoglycoside-modifying enzymes chemically modifies aminoglycosides This stops 30S ribosomal subunit to bind effectively, due to which inhibitory effect on protein synthesis terminates, leading to resistance development (Parveen et al. 2025). Biofilm formation is also a resistance mechanism carried out by *P. aeruginosa*. Highly structured biofilms stop antibiotics to enter. Additionally, biofilm matrices isolate antimicrobial agents through interactions with cyclic glucans, thereby limiting their effective concentration. The development, maturation, and maintenance of biofilms are tightly regulated by quorum-sensing networks and global regulatory systems, including the GacS/GacA pathways,

leading to enhanced adaptive resistance (Elfadadny et al. 2024). **Figure 2** illustrates general multiple resistance mechanisms in a bacterial cell. In Gram-negative bacteria, AMR occurs through comprehensive mechanism and regulatory responses, where genetic plasticity, structural defense mechanisms, and adaptive regulatory response takes part for its survival and growth. Short-term physiological changes integrated with long-term genetic shifts makes these type of bacteria highly adaptable to antibiotic pressure (Gauba and Rahman 2023). In case of *E. coli*, it is evident for causing urinary tract infections (UTIs) worldwide. The global predominance of *E. coli* has been consistently reported across community-acquired infections. Resistance is reported for FQs, particularly ciprofloxacin in many studies, where high resistance rates are also highly observed trimethoprim-sulfamethoxazole and ampicillin, which are of particular concern because these drugs have traditionally been recommended for first-line therapy for uncomplicated UTIs. Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggest avoiding antibiotics when local resistance rates exceed 20% (Kapesa, Mumbula, and Kwenda 2025). While these guidelines apply primarily to community-acquired pathogens like *E. coli*, hospital-associated Gram-negative bacteria such as *P. aeruginosa* present additional challenges. In case of *P. aeruginosa*, a Gram-negative bacterium is a major nosocomial pathogen due to its intrinsic resilience and adaptability mechanisms. It is reported to cause UTIs, bloodstream infections, wound infections, and bone structure infections, particularly among immunocompromised patients or those with breached epithelial barriers. The 6.5 Mbp of genome contributes to its survival in different growing conditions in host tissues, water, and soil. This makes it more persistent to grow in clinical settings such as on catheters, ventilators, and endotracheal tubes. Its resistance to antibiotics are generally higher, where MDR *P. aeruginosa* is resistant against more three or more antimicrobial classes, whereas, in case of extensively drug-resistant (XDR) strains are resistant to nearly all antibiotics. Global surveillance reveals considerable geographic heterogeneity in MDR and XDR prevalence, with hospital-acquired infections demonstrating the highest rates (Alharbi et al. 2025). According to the World Health Organization (WHO), the strains of *P. aeruginosa* with acquired immunity to carbapenems, a class of "last-resort" broad-spectrum-lactam antibiotics, often result in MDR and are classified as “critical priority” pathogens. These bacteria pose a critical threat to human health due to high morbidity and limited treatment (Huang et al. 2023). Apart from hospital-associated pathogens like *P. aeruginosa*, other Gram-negative bacteria such as *Salmonella* species are a significant concern, particularly in the context of foodborne infections. A gram-negative bacterium, an anaerobic and rod-shaped bacteria, family is responsible for a broad spectrum of foodborne illnesses in humans and animals. *Salmonella enterica (S. enterica)* is reported as most clinically significant, causing both non-typhoidal Salmonella (NTS) gastroenteritis and systemic typhoid fever (Billah and Rahman 2024). Transmission primarily occurs through contaminated food or water, contact with infected animals, and poor sanitation. The mechanism of resistance due to excess use of antibiotics includes chromosomal mutations, horizontally acquired genes, and mobile genetic elements (MGEs). Intrinsic resistance mechanisms also facilitate resistance in *Salmonella* strains. Additionally, resistance determinants confer MDR through conjugation, transformation, transduction, and horizontal gene transfer (HGT) (Kumar et al. 2025). These chromosomal mutations and HGT determinants confirm multifactorial nature of *Salmonella* resistance to antibiotics. β-lactam resistance mediates through the production of β-lactamase enzymes, including extended-spectrum β-lactamases (ESBLs) such as *blaTEM* and *blaCTX-M genes*, as well as AmpC enzyme, reduces drug affinity. The chemical alterations of antibiotics like

gentamicin and kanamycin causes loss of effective binding to the ribosomal sub-unit of bacteria. Resistance particularly in FQs is driven by point mutations in the QRDRs affecting DNA gyrase and topoisomerase 4. The increase in effect is done by plasmid-mediated *qnr* genes and overexpression of efflux pumps such as AcrAB-TolC. Tetracycline resistance is mediated by efflux systems and ribosomal protection proteins. Macrolide resistance occurs through ribosomal modifications, reducing drug binding and limiting the efficacy of antibiotics such as azithromycin. Finally, carbapenem resistance is mediated through the production of carbapenemases, including MBLs, and porin alterations reduces drug uptake, contributing to nosocomial outbreaks in hospital settings. (Giuriatti et al. 2017, Khalifa et al. 2021). Collectively, these findings on mechanisms underscore the complex, MDR phenotype of *Salmonella* and highlight the challenges faced in clinical management and infection control (Kumar et al. 2025). In contrast to Gram-negative pathogens, Gram-positive bacteria rely on their thick peptidoglycan layer and distinct resistance mechanisms to cause a wide range of infections. The structural features coupled with resistance mechanisms results in wide range of infections, from mild skin infections to life-threatening diseases like pneumonia, endocarditis, and sepsis. Clinically significant species include *Staphylococcus aureus (S. aureus)* and *Streptococcus pneumoniae (S. pneumonia)* (Rajput, Nahar, and Rahman 2024). Resistance mechanisms include mutations in DNA gyrase and efflux pumps. Mutations in *gyrA* causes high-level resistance, including modifications where Ser-84 is substituted by Leu and Glu-88 is substituted by Lys. Topoisomerase 4 is the primary target of FQs in *S. aureus*, with double mutants exhibiting markedly higher MICs compared to single mutants, while the diversity in MICs among strains suggests additional mechanisms, such as efflux pumps, contribute to resistance. In *S. pneumonia*, FQs resistance similarly involves mutations in topoisomerase 4 subunits encoded by *parC* and *parE*, which are often co-targeted alongside DNA gyrase. Alterations in these genes reduces drug binding, contributing to reduced susceptibility. This highlights the conserved role of topoisomerase 4 mutations across Gram-positive respiratory pathogens in mediating quinolone resistance (Goswitz et al. 1992). Similarly, FQ resistance in *Mycobacterium tuberculosis (M. tuberculosis)* involves mutations in DNA gyrase, highlighting conserved mechanisms. *M. tuberculosis* majorly causes tuberculosis (TB), where first-line antibiotics are generally used. MDR in TB, particularly in FQs causes due to mutations in the *gyrA* gene at codons 88 to 94. This modifies the binding site of DNA gyrase and drug loses its efficacy. These *gyrA* mutations are critical molecular markers for identifying FQ-resistant TB strains, guiding both treatment strategies and molecular diagnostic testing (Chien et al. 2016). **Table 1** summarizes targets, resistance mechanisms, and the clinical relevance of various bacterial strains.

4. Discussion

In this review, resistance mechanisms of various bacteria against DNA gyrase inhibitors were explored, where it is found to be a global health challenge. Resistance mechanisms against various bacterial classes, such as Gram-negative, Gram-positive, and acid-fast bacteria provides an insight that it emerges through a combination of target-site mutations, efflux pump dysregulation, and plasmid-mediated gene transfer (Kakoullis et al. 2021). Under these mechanisms, *E. coli* was discussed where point mutations in QRDR of *gyrA* and *gyrB* found responsible for reducing binding affinity of drug. A role of plasmid-mediated determinants in protection of DNA gyrase and modifying antibiotic through substrate binding provides molecular insights (Hooper and Jacoby 2015). These molecular mechanisms with similar patterns are observed in *S. pneumonia* where parC and parE mutations in topoisomerase 4 contribute to FQ resistance, and in *M. tuberculosis*, where

gyrA mutations confer FQ resistance (Collins and Osheroff 2024). Resistance mechanisms facilitated by overexpression of efflux pumps confirm its role in enhancing resistance where system in Gram-negative bacteria, regulated by mutations in *acrA*, *acrB*, and *tolc* genes demonstrates how bacteria integrate physiological responses with genetic adaptations. Biofilm formation in pathogens like *P. aeruginosa* and *E. coli* adds another layer of tolerance, limiting drug penetration and promoting survival under antibiotic pressure. HGT accelerates the dissemination of MDR and XDR strains across hospital, community, and environmental settings. Patterns of species-specific resistance provide insights in clinical settings. In different kinds of infections, MDR *E. coli* complicates UTIs, *P. aeruginosa* persists in nosocomial infections through intrinsic resistance mechanisms, *S. aureus* demonstrates how topoisomerase mutations in Gram-positive bacterial species drive resistance to respiratory and other infections. Meanwhile, FQ resistance in *M. tuberculosis* underscores the public health threat of limited therapeutic options. Collectively, these findings show that resistance is a dynamic process shaped by genetic, physiological, and ecological factors, rather than a single mutation (Muteeb et al. 2025). The interplay of selective pressure from antibiotic misuse, mobile resistance elements, and bacterial adaptability emphasizes the need for integrated strategies, including antibiotic stewardship, molecular surveillance, and development of novel therapeutics (Ramanisankar et al. 2025). Understanding these mechanisms provides a foundation for targeted interventions to mitigate the global spread of MDR infections and improve clinical outcomes.

5. Conclusion

Combination of mechanisms including target-site mutations, efflux pump overexpression, plasmid-mediation, and adaptive physiological mechanisms results in resistance among different bacterial species. Gram-positive and Gram-negative bacteria as well as acid-fast and other bacteria include species specific strategies to evade DNA gyrase inhibitors. HGT and selective pressure from antibiotic misuse accelerate the spread of MDR strains, complicating treatment and infection control. Understanding these molecular mechanisms is critical for guiding antibiotic stewardship, informing clinical decision-making, and developing novel therapeutic strategies. Continued surveillance and integrated interventions are essential to mitigate the global threat posed by MDR bacterial infections.

Conflict of Interest

The authors have no competing interests to declare.

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SS conceptualized and organized the study, and SS and AN drafted the manuscript. Both authors reviewed and approved the final version of the manuscript.

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