Emerging Trends in Quinolone Resistance Among Urinary Pathogens: A Brief Review

ABSTRACT

Urinary tract infections (UTIs) present a significant global health challenge, Intensified by the high level of antimicrobial resistance, particularly to quinolone antibiotics. This brief review synthesizes recent literature to elucidate the prevalence and mechanisms of quinolone resistance, with a focus on plasmid-mediated quinolone resistance (PMQR), among UTI-causing pathogens. Highlighting the genetic basis of resistance, including mutations in DNA gyrase and efflux pump regulation genes, as well as the role of plasmid-mediated mechanisms such as 'qnr' genes, the review underscores the clinical implications of quinolone resistance in UTI management. Understanding these emerging trends is urgently required for improving antimicrobial management strategies and guiding effective interventions to control the spread of quinolone resistance among urinary pathogens.

Keywords:

- *Quinolone resistance*
- *Urinary pathogens*
- *Antibiotic resistance*
- *Urinary tract infections (UTIs)*
- *Multidrug resistance (MDR)*
- *Extensively drug-resistant (XDR)*
- Pan-drug-resistant (PDR)
- Antimicrobial stewardship

ABBREVIATIONS

UTIs: Urinary tract infections

PMQR: Plasmid-mediated quinolone resistance

ESBL: Extended-spectrum beta-lactamase

CREc: Carbapenem-resistant Escherichia coli

MDR: Multidrug resistance

XDR: Extensively drug-resistant

PDR: Pan-drug-resistant

WGS: Whole-genome sequencing

ARGs: Antibiotic resistance genes

ExPEC: Extraintestinal pathogenic E. coli

1. INTRODUCTION

Urinary tract infections (UTIs) are prevalent bacterial infections affecting millions globally, posing significant public health challenges.[1][2]The World Health Organization recognizes UTIs as a widespread concern, impacting morbidity, healthcare costs, and escalating antimicrobial resistance rates.[3] UTIs are common in Asian countries, with escalating antibiotic resistance rates, signaling the emergence of spreading resistant strains.[4] With the trend of UTIs becoming increasingly common, there is a persistent need for improved management strategies amidst rising antibiotic resistance. Gram-negative bacteria are the primary cause of UTIs due to their ability to adhere to and colonize the urinary tract mucosa, thereby initiating infections.[5]Among antibiotic-resistant clinical pathogens, *E. coli* and *Klebsiella spp* are frequently encountered.[6][7]

Quinolone antibiotics, such as norfloxacin and nalidixic acid, have been the primary choices for treatment due to their broad spectrum of activity against uropathogens. However, their extensive use has led to the emergence and spread of resistant strains, diminishing treatment efficacy.[8] Quinolones function by inhibiting bacterial DNA replication and repair; however, misuse has resulted in rising resistance, primarily through mutations in DNA gyrase and efflux pump regulation genes.[9][10]Additionally, plasmid-mediated resistance mechanisms, such as *qnr* genes, contribute to multidrug resistance, complicating treatment processes.[11][12]The escalating severity of quinolone resistance calls attention to the urgent need to understand the genetic basis of resistance mechanisms in microbes. [13]This constant change in antimicrobial resistance mechanisms and the lack of new antibiotics to tackle this problem need to be addressed immediately.[14][15]

This review aims to assess the prevalence of quinolone resistance, particularly plasmid-mediated quinolone resistance (PMQR), in bacteria causing UTIs. A comprehensive search across reputable databases such as PubMed, Google Scholar, and ScienceDirect, as well as relevant scientific journals including those from the American Society of Microbiology (ASM), was conducted to gather pertinent literature. Through this qualitative analysis of current literature, the study aims to provide insights into the extent of quinolone resistance in UTI-causing microbes, thereby shedding light on potential implications for clinical management and public health.

2. Antibiotic resistance in Urinary Tract Infections

Antibiotic resistance presents a significant global public health challenge, particularly pronounced in India. With an infectious disease mortality rate of 416.75 per 100,000 persons in 2016, India faces a pressing concern regarding the spread of resistant pathogens. Various factors, including inadequate public health infrastructure, hospital-acquired infections, high rates of infectious diseases, and easy access to inexpensive antibiotics, contribute to this threat. As a result, there's a growing burden of untreatable conditions like neonatal sepsis and healthcare-associated infections, underscoring the immediate need for effective strategies to combat antibiotic resistance in the country.[16]

In 2023, Sharma et al. highlighted the critical threat posed by antimicrobial resistance (AMR) to global public health, particularly within India's healthcare system. With its dense population, significant disease burden, and diverse healthcare practices, India stands at a crucial crossroads in combating AMR on a global scale. The consequences of this crisis are far-reaching, impacting healthcare delivery, mortality rates, and the achievement of Sustainable Development Goals. Addressing AMR in India requires a comprehensive approach, including robust regulatory frameworks, improved diagnostics, heightened public awareness, and research into new antimicrobials.[17]

The study of Hilt et al., in 2023 mentioned the classification of UTIs, introducing newer definitions such as "acute simple cystitis" and "acute complicated UTI" based on the extent of infection and severity of illness. This shift in terminology reflects advancements in clinical practice and antimicrobial uses, emphasizing the importance of newer treatment approaches to individual patient presentations. By acknowledging the limitations of traditional classifications and advocating for more nuanced approaches, the study contributes to ongoing efforts to optimize UTI management and combat antimicrobial resistance.[18]

2.1. Quinolone-resistance in urinary pathogens

A study conducted in a tertiary care hospital in Amritsar, Punjab, India, investigated the prevalence and antibiotic resistance patterns of uropathogens among female patients with urinary tract infections (UTIs). *Escherichia coli* emerged as the predominant uropathogen, followed by *Klebsiella spp* and *Enterobacter spp*. The study revealed eight isolates with multi-drug resistance, underscoring the growing challenge of antibiotic resistance. Notably, gentamicin, imipenem, and meropenem showed efficacy against these resistant strains. The detection of the quinolone-resistant gene *qnrB* in all extended-spectrum β-lactamase (ESBL)-positive isolates provided valuable insights into the genetic mechanisms contributing to resistance. These findings emphasize the significance of epidemiological data in guiding empirical antibiotic treatment for UTIs and highlight the importance of ongoing surveillance and prudent antibiotic use in clinical practice.[19]

In 2023 cross-sectional study explored the correlation between biofilm formation and multidrug resistance in uropathogenic*Escherichia coli* (UPEC) strains isolated from urine samples. Results show that 23.92% of UPEC isolates are multidrug-resistant, with 36.06% exhibiting potent biofilm-forming capabilities. These biofilm-producing strains display resistance to commonly using UTI antibiotics but are sensitive to imipenem and meropenem. The study highlights the significance of biofilm formation in antimicrobial resistance and suggests improved strategies for managing biofilm-associated UTIs. Advanced techniques like VITEK R2 Compact and 16S rRNA gene sequencing were used to confirm and characterize the isolated *E. coli* biofilms, contributing valuable insights into addressing multidrug resistance in uropathogenic*E. coli* strains.[20]

A study examined the prevalence and antibiotic resistance patterns of uropathogens causing urinary tract infections (UTIs). *E. coli* is identified as the primary uropathogen, followed by *Klebsiella species*, confirmed through gram staining, microscopy, and biochemical characterization. Alarmingly, *E. coli* shows significant resistance to Nitrofurantoin, Ciprofloxacin, and Co-Trimoxazole, resulting in a 36% multidrug resistance (MDR) rate. Extensively drugresistant (XDR) and pan-drug-resistant (PDR) strains are reported, particularly in *Klebsiella* and *Enterobacter. Staphylococcus* exhibits increased resistance, while *Pseudomonas* and *Proteus* show negligible drug resistance. Molecular investigations revealed a high frequency of *gyr-A*, *tet-A*, *aac*(6′)-*Ib* genes, and β-lactamase gene presence in the uropathogens. This analysis highlights the growing antibiotic resistance crisis in uropathogens, emphasizing the need for effective strategies to manage drug-resistant UTIs. The findings provide valuable insights for public health interventions and antibiotic stewardship efforts.[21]

In a rural area of central India, a study examines the presence of extended-spectrum β-lactamase (ESBL)-producing commensal *Escherichia coli* in healthy school children, highlighting their potential as reservoirs for antibiotic resistance genes within the community. The investigation reveals a significant prevalence of CTXM-15, TEM-1, OXA-1, and SHV-12 genes associated with cephalosporin resistance among these isolates. Additionally, all isolates carry the *aac*(6')-ib-cr gene, with a subset being *qnrS* positive, indicating plasmid-mediated quinolone resistance. The presence of virulence genes like *fluA*, *fluB*, *eae*, and *daaE* underscores the dual nature of these commensal *E. coli* strains, serving as potential reservoirs for both antibiotic resistance and virulence factors linked to urinary tract and diarrheal infections. The study underscores the necessity for ongoing surveillance and antimicrobial stewardship in communities to mitigate the potential spread of antibiotic resistance among healthy populations.[22]

A study conducted whole-genome sequencing (WGS) on 103 carbapenem-resistant *Escherichia coli* (CREc) urinary isolates to analyze fluoroquinolone-resistant determinants. Predominantly, ST410, followed by ST405 and ST361, with Clermont phylogroup C, were identified as the most frequent. The presence of NDM-5 and CTX-M-15 genes

significantly contributed to extensive resistance, particularly against ciprofloxacin and levofloxacin. The recurrent coexistence of aac(6′)-Ib and blaCTX-M-15 underscored the genetic complexity of these isolates. Additionally, the study explored the complete genomes of five urinary CREc isolates, elucidating the plasmid types harboring blaNDM-5 or blaNDM-3 and their association with other resistance genes. These findings highlight the urgency for efficient strategies and control policies to mitigate the spread of fluoroquinolone-resistant CREc strains, offering valuable insights for ongoing efforts in monitoring and combating antimicrobial resistance.[23]

The resistance patterns among *Enterobacteriaceae* isolated from urinary tract infections (UTIs) exhibited High rates of quinolone resistance among ESBL-producing isolates highlighting the increasing challenge of antibiotic resistance in this clinical context. The identification of *PMQR* genes, notably *aac*(6′)-Ib-cr, in a significant proportion of samples, adds complexity to the resistance landscape. Associations between *PMQR* genes and *ESBL*s, particularly *blaCTX-M*-15 and *blaTEM*-116, underscore the interconnectedness of different resistance mechanisms. These findings stress the urgent need for vigilant antibiotic stewardship and surveillance to control the spread of resistant strains in this region. The study significantly enhances our understanding of resistance gene prevalence and associations in *Enterobacteriaceae* from UTIs.[24]

Research conducted in southwest Iran addresses the pressing issue of antibiotic resistance in *Escherichia coli*, as a key opportunistic pathogen causing urinary tract infections (UTIs). The study explores the extent of antibiotic resistance to quinolones and investigates the prevalence of *qnr*genes (A, B, and S) in both extended-spectrum beta-lactamase (ESBL) and non-ESBLproducing*E. coli* strains isolated from UTI-diagnosed patients. The findings reveal concerning levels of resistance, particularly against nalidixic acid, highlighting the necessity for robust antibiotic stewardship in Ahvaz's hospitals, Khuzestan province. The identification of *qnr* genes, notably *qnrS*, among ESBL-producing isolates raises alarm about the interconnectedness of various resistance mechanisms. This study contributes valuable insights into the antibiotic resistance landscape of *E. coli* associated with UTIs in southwest Iran, emphasizing the need for further research to comprehensively assess the gravity of quinolone resistance in the country and develop effective strategies against its spread among nosocomial pathogens.[25]

Alhazmi et al., (2023) conducted a cross-sectional study in Jazan Province, Kingdom of Saudi Arabia, which reveals the significant impact of urinary tract infections (UTIs) on the healthcare system, constituting 10% of all infections and ranking as the second leading cause of emergency department admissions. With 1082 urinary bacterial samples analyzed, Gram-negative bacteria, particularly *Escherichia coli*, dominate the causative pathogens. Alarmingly, 30.13% of cases exhibit extended-spectrum beta-lactamase (ESBL) resistance, and multidrug-resistant organisms contribute to approximately 35% of reported cases. The study identifies a seasonal pattern, with heightened UTI incidence in September. These findings underscore the urgent need for targeted interventions and antimicrobial stewardship programs to address the prevalence of antibiotic-resistant microbes and mitigate the impact of UTIs.[26]

Another study focused on a thorough analysis of *Escherichia coli* isolates obtained from urinary tract infections in Kerala, South India. The research aimed to understand the phylogenetic groups, antibiotic resistance patterns, presence of antibiotic resistance genes (ARGs), integrons, extraintestinal virulence genes, and the genetic diversity among 100 *E. coli* isolates. The isolates exhibited varying degrees of resistance, with ampicillin resistance being the most prevalent, followed by resistance to cefoxitin, cefpodoxime, nalidixic acid, trimethoprim, and cotrimoxazole. Remarkably, 96% of the isolates demonstrated multidrug resistance (MDR), and 86% harbored ARGs, while 32% carried integron 1 (int1). The majority of the isolates (79%) were classified as extraintestinal pathogenic *E. coli* (ExPEC), with 86% of these ExPEC strains containing ARGs. Additionally, one isolate exhibited extensive drug resistance (XDR). The study highlighted a significant correlation between the presence of virulence genes and antibiotic resistance. The observed high genetic diversity among ARG-harboring*E. coli* isolates emphasizes the intricate dynamics of antibiotic resistance in urinary tract infections caused by *E. coli*, underscoring the importance of understanding this association for effective treatment strategies. [27]

3. CONCLUSIONS

The escalating prevalence of quinolone resistance among urinary pathogens is anarduous challenge in the management of urinary tract infections (UTIs). Our review underscores the urgent need for systematic strategies to address this growing threat to public health. The studies highlighted in this review reveal trends in antibiotic resistance, where the emergence of quinolone-resistant genes poses significant clinical and public health concerns. The detection of plasmid-mediated quinolone resistance (*PMQR*) genes, such as *qnrB* and *aac*(6′)-Ib-cr, in UTI-causing pathogens,highlights the genetic complexity underlying antibiotic resistance. Urgent interventions are needed to fight the spread of resistant pathogens and preserve the efficacy of existing antibiotics. Collaborative efforts among healthcare providers, policymakers, researchers, and the community are essential to address this global public health challenge effectively. By implementing evidence-based interventions and fostering antimicrobial practices, we can strive towards preserving the effectiveness of antibiotics and ensuring optimal outcomes for patients with UTIs.

AUTHORS' CONTRIBUTIONS

Rasmi T.R. designed the study, performed the preliminary analysis and reading, sorted the studies, and wrote the first draft of the manuscript. Dr. Pavan Chand Attavar and M Shashidhar Kotianmanaged the analyses of the study. Sona P.Hydrosemanaged the literature searches.Delna N.S. managed the final corrections and publication procedures. All authors read and approved the final manuscript.

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