Antibiotic Resistance Patterns and Molecular Determinants of Fluoroquinolone Resistance Among Urinary Escherichia coli Isolates – A Comparison of Disc Diffusion and MIC Methods

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ABSTRACT

Background: Urinary tract infections remain one of the major public health concerns worldwide, for which Escherichia coli (E. coli) is the predominant causative organism. The study aims to assess the resistance patterns of E. coli in urinary, identify fluoroquinolone-associated gyrA mutations, and evaluate their association with phenotypic resistance profiles. **Methods & Materials:** This cross-sectional study was conducted at Sir Salimullah Medical College and Mitford Hospital, Dhaka, from January to December 2020. 229 urine samples collected by purposive sampling were analyzed for this study. Identification of the bacterial isolates was performed by standard biochemical tests; antimicrobial susceptibility testing was done according to CLSI guidelines by disc diffusion and agar dilution methods to determine the MIC. Detection of mutations in the gyrA gene that confer resistance to quinolones was performed with the use of the PCR-RFLP methodology, with HinfI restriction enzyme digestion targeting codons 83 and 87. **Results:** Among the 138 culture-positive samples, E. coli constituted 81.8% of the total isolates. The overall fluoroquinolone resistance rate was 52.2% as determined by the disc diffusion method. The ciprofloxacin MICs were ≥4 µg/ml in 43.4% of the isolates as determined by MIC testing. Molecular analysis detected gyrA mutations in 55.7% of all E. coli isolates. 37.1% mutations were shown at both Ser83 and Asp87 codons. 92.1% of isolates with gyrA mutations showed a phenotypic ciprofloxacin resistance that established a strong genotype-phenotype correlation. Only double mutations were associated with higher MIC values (≥8 µg/ml) and a complete resistance phenotype, while single mutations were associated with lower MIC ranges (0.25-4 µg/ml). **Conclusion:** This study documents high fluoroquinolone resistance rates among urinary E. coli isolates, largely driven by double mutations in the gyrA gene. These findings highlight the clinical relevance of molecular surveillance in guiding empirical treatment decisions due to its close association with resistance phenotypes.

Keywords: *Escherichia coli, Fluoroquinolone resistance, gyrA mutations, Urinary tract infection, PCR-RFLP*

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INTRODUCTION

Urinary tract infections are among the most common bacterial infections worldwide, with approximately 150 million cases annually, placing a significant burden on healthcare systems [1]. *E. coli* remains the most dominant uropathogen, causing the majority of community-acquired infections, and a high proportion of hospital-acquired episodes further solidifies its dominance within both ambulatory and inpatient parameters [2]. This is attributed to its vast arsenal of virulence factors and inherent adaptability, which enable its persistence and global clinical relevance. An increasingly antimicrobial-resistant nature of uropathogenic *E. coli* populations has emerged as a significant therapeutic challenge, especially in developing countries where widespread antibiotic availability and frequent misuse expedite the emergence of resistance [3]. Fluoroquinolones, such as ciprofloxacin and levofloxacin, have long been used as first-line agents for the management of urinary tract infection, based on their broad antimicrobial spectrum, strong tissue penetration, and convenient oral dosing characteristics [4]. Their bactericidal action is via inhibition of bacterial DNA gyrase and topoisomerase IV, enzymes that are considered important for DNA supercoiling and chromosomal replication [5]. However, increasing and often inappropriate fluoroquinolone consumption is being paralleled by rising resistance rates worldwide, with surveillance reports noting resistance levels of 15-50% across different regions and particularly high rates in South Asia [6]. Resistance of *E. coli* to fluoroquinolones is mediated through complex mechanisms involving chromosomal mutations, efflux pump activation, and plasmid-borne resistance determinants [7]. Chromosomal alterations within the quinolone resistance-determining regions of target genes constitute a core mechanism for high-level resistance. The most critical mutation hotspots within the gyrA gene encoding the A subunit of DNA gyrase involve codons 83 and 87, with amino acid substitutions like Ser83Leu and Asp87Asn commonly reported [8]. Such modifications decrease the affinity of fluoroquinolones for their target and thus reduce drug efficacy. Accumulation of multiple mutations is strongly associated with rising minimum inhibitory concentrations and increased risk of therapeutic failure [9]. Indeed, reliable antimicrobial susceptibility testing is still crucial for appropriate patient management and to inform the development of effective antimicrobial stewardship programs. Disc diffusion techniques are still widely used because of their ease and low cost, while minimum inhibitory concentration testing provides more accurate quantification of drug activity and better prediction of clinical outcome [10]. Recent developments in molecular diagnostics have facilitated the use of PCR-based restriction fragment length polymorphism analysis to rapidly detect resistance-conferring mutations and improve epidemiological typing capability [11]. There is a need to understand genotype-phenotype relationships to enable the prediction of treatment outcomes and to inform evidence-based antibiotic policies. It is within this context, the study aims to determine local resistance patterns among urinary *E. coli* isolates, to determine fluoroquinolone-related gyrA mutations, and to assess their association with the

corresponding phenotypic resistance profile.

METHODS & MATERIALS

This cross-sectional study was conducted in the Department of Microbiology at Sir Salimullah Medical College and Mitford Hospital, Dhaka, over a 12-month period from January to December 2020. The study population consisted of patients of all ages and both sexes attending the microbiology department from both inpatient and outpatient units for urine culture and antibiotic susceptibility testing. Individuals with clinically suspected urinary tract infection (UTI) were eligible for inclusion, while patients who had taken antibiotics within the preceding 14 days, those on current antibiotic therapy, and catheterized urine samples were excluded. A total of 229 urine samples were ultimately collected through purposive sampling. Clinical and demographic information, including age, sex, duration of hospitalization, and prior antibiotic history, was collected using a structured questionnaire. Written informed consent was obtained from each participant or their guardian, and ethical approval was granted by the Ethical Review Committee of Sir Salimullah Medical College and Mitford Hospital. Approximately 10 ml of midstream urine was collected under aseptic conditions. Primary culture was performed on MacConkey agar and Blood agar, followed by incubation at 37°C for 24 hours [12]. Bacterial isolates were identified through standard biochemical tests using Kligler Iron Agar, Simmons' citrate agar, and Motility-Indole-Urea media [13]. Antimicrobial susceptibility testing was performed on Mueller-Hinton agar following CLSI guidelines [14]. Detection of gyrA gene mutations associated with quinolone resistance was performed using PCR-RFLP [15]. DNA was extracted using the Monarch genomic DNA purification kit [16]. A 164-bp fragment of the gyrA gene encompassing codons 83 and 87 was amplified using allele-specific primers. PCR was carried out in a 25 µl reaction mixture, and amplification products were subjected to HinfI restriction enzyme digestion [17]. Electrophoresis on a 3 percent agarose gel was used for the interpretation of band patterns, allowing discrimination between wild-type and mutated alleles at Ser83 and Asp87. ATCC E. coli 25922 served as the control strain [18]. All collected data were entered and analyzed using SPSS version 26.

RESULTS

Table I represents the overall culture yield and distribution of bacterial pathogens isolated from 229 urine samples. Out of these, 138 samples (60.2%) showed positive bacterial growth, and *E. coli* was the predominant isolate at 81.8%, followed by *Klebsiella* species (8.7%), *Pseudomonas* (6.5%), and other less common organisms.

Table I
Rate of Growth Yielded from Urine Culture and Distribution of Organisms Isolated (*n*=229).

Variable	Category	No. of Isolates	Percentage
Growth Yield	Positive	138	60.2%
	Negative	91	39.7%
Bacterial Isolates (n=138)	E. coli	113	81.8%
	Klebsiella	12	8.7%
	Pseudomonas	9	6.5%
	Citrobacter	2	1.4%
	Proteus	1	0.7%
	Staphylococcus aureus	1	0.7%

Table II shows the overall susceptibility pattern of 113 *E. coli* strains against 16 different antimicrobial agents. Of note are the high resistance rates to nalidixic acid, at 72.6%; aztreonam, 71.7%; amoxiclav, 69%; and cefuroxime, 67.3%. On the other hand, carbapenems (imipenem and meropenem), and amikacin, had resistance rates of less than 15%. For most antibiotics, the proportion in the intermediate category was low, indicating well-delineated susceptible and resistant populations.

Table II
Antibiotic Susceptibility pattern among *E. Coli* (*n*=113).

Antimicrobial Agents	Sensitive (n) (%)	Intermediate (n) (%)	Resistant (n) (%)
Mecillinam (10 µg)	66 (58.4%)	3 (2.7%)	44 (38.9%)
Ceftazidime (30µg)	40 (35.4%)	4 (3.5%)	69 (61.1%)
Cefuroxime (30µg)	31 (27.4%)	6 (5.3%)	76 (67.3%)
Ceftriaxone (30µg)	48 (42.5%)	4 (3.5%)	61 (54%)
Cefixime (5µg)	39 (34.5%)	6 (5.3%)	68 (60.2%)
Nalidixic Acid (30µg)	26 (23%)	5 (4.4%)	82 (72.6%)
Ciprofloxacin (5µg)	48 (42.5%)	6 (5.3%)	59 (52.2%)
Levofloxacin (5µg)	76 (67.3%)	2 (1.8%)	35 (31%)
Nitrofurantoin (300µg)	86 (76.1%)	0 (0%)	27 (23.9%)
Gentamicin (10µg)	83 (73.5%)	4 (3.5%)	26 (23%)
Amikacin (30µg)	96 (85%)	3 (2.7%)	14 (12.4%)
Co-trimoxazole (1.25/23.75µg)	50 (27.4%)	6 (5.3%)	57 (50.4%)
Amoxiclav (20/10µg)	31 (27.4%)	4 (3.5%)	78 (69%)
Meropenem (10µg)	105 (92.9%)	0 (0%)	8 (7.1%)
Imepenem (10µg)	100 (88.5%)	0 (0%)	13 (11.5%)
Aztreonam (30µg)	30 (26.5%)	2 (1.8%)	81 (71.7%)

Table III represents the distribution of ciprofloxacin minimum inhibitory concentration (MIC) values amongst the *E. coli* isolates by the agar dilution method. MIC values showed a bimodal distribution pattern, where the peaks at high concentrations represent resistant populations (16 µg/ml: 20.4%, 8 µg/ml: 16.8%), while those at lower concentrations represent susceptible strains (0.015 µg/ml: 9.7%, 0.007 µg/ml: 7.9%), reflecting the distinct genetic basis for resistance mechanisms.

Table III
MIC values of ciprofloxacin by agar dilution method (*n*=113).

MIC value of Ciprofloxacin (µg/ml)	n	%
16 µg/ml	23	20.4%
8 µg/ml	19	16.8%
4 µg/ml	7	6.2%
2 µg/ml	6	5.3%
1 µg/ml	2	1.7%
0.5 µg/ml	4	3.5%
0.25 µg/ml	11	9.7%
0.12 µg/ml	9	7.9%
0.06 µg/ml	6	5.3%
0.03 µg/ml	6	5.3%
0.015 µg/ml	11	9.7%
0.007 µg/ml	9	7.9%

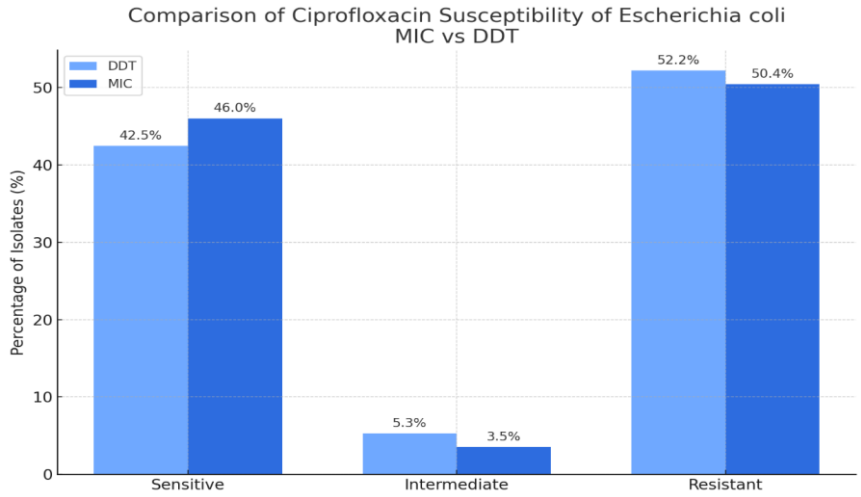

Figure 1 Comparison of susceptibility of *E. coli* against ciprofloxacin by agar dilution method (MIC) and disc diffusion technique (DDT) (*n*=113)

Figure 1 compares ciprofloxacin susceptibility of 113 urinary *E. coli* isolates by disc diffusion and MIC methods, showing broadly concordant categorizations, with MIC classifying slightly more isolates as sensitive and fewer as resistant, and minimal intermediate susceptibility in both assays.

Table IV shows the differential resistance patterns between ciprofloxacin-resistant and ciprofloxacin-sensitive *E. coli* isolates. Remarkably, all ciprofloxacin-resistant isolates demonstrated concurrent resistance to nalidixic acid at 100%, probably indicating related resistance mechanisms. Cross-resistance was particularly evident with β-lactams and aztreonam, while carbapenems retained activity against both groups.

Table IV
Comparison of antibiotic resistance profile between ciprofloxacin-resistant and ciprofloxacin-sensitive Escherichia coli isolates (*n*=113).

Antimicrobial agents	Ciprofloxacin resistant (n=61)	Ciprofloxacin sensitive (n=52)
Mecillinam (10 µg)	28 (45.9%)	19 (36.5%)
Ceftazidime (30µg)	37 (60.7%)	36 (69.2%)
Cefuroxime (30µg)	46 (75.4)	36 (69.2%)
Ceftriaxone (30µg)	30 (49.2%)	35 (67.3%)
Cefixime (5µg)	43 (70.5%)	31 (59.6%)
Nalidixic Acid (30µg)	61 (100%)	26 (50%)
Levofloxacin (5µg)	16 (26.2%)	21 (40.4%)
Nitrofurantoin (300µg)	19 (31.1%)	8 (15.4%)
Gentamicin (10µg)	9 (14.8%)	21 (40.4%)
Amikacin (30µg)	5 (8.2%)	12 (23.1%)
Co-trimoxazole (1.25/23.75µg)	35 (57.4%)	28 (53.8%)
Amoxiclav (20/10µg)	44 (72.1%)	38 (73.1%)
Meropenem (10µg)	3 (4.9%)	5 (9.6%)
Imepenem (10µg)	4 (6.6%)	9 (17.3%)
Aztreonam (30µg)	45 (73.8%)	38 (73.1%)

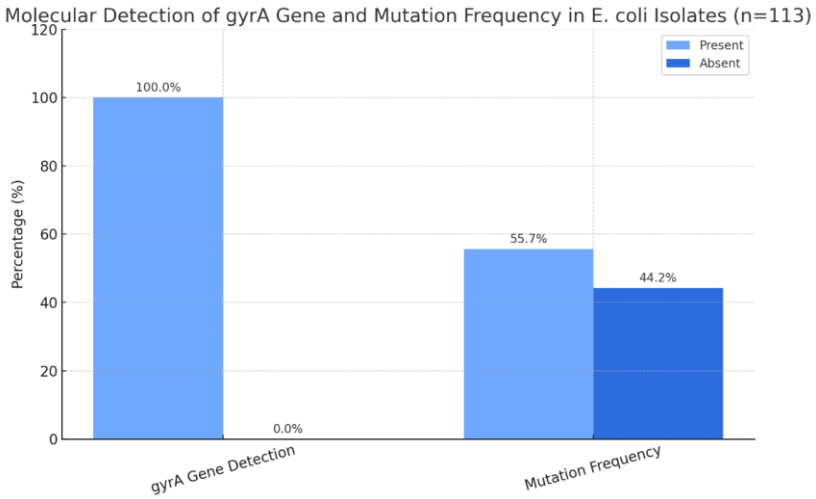

Figure 2 Molecular detection and mutation frequency of the gyrA gene in *E. coli* isolates (*n*=113).

Figure 2 depicts the molecular detection results, indicating that 55.7% of *E. coli* isolates carried gyrA gene mutations, while 44.2% exhibited a wild-type genotype. The high percentage of mutated strains points out the wide dissemination of chromosomally mediated fluoroquinolone resistance within the study population and underlines the value of molecular surveillance in understanding the epidemiology of resistance.

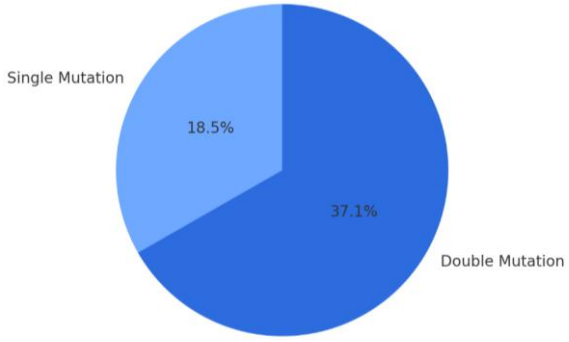

Figure 3 Type of gyrA Mutation gene among the *E. coli* Isolates.

Figure 3 reveals the kinds of gyrA mutations identified, showing that double mutations at both Ser83 and Asp87 codons were predominant, at 37.1% of mutated strains, while single mutations solely at Ser83 occurred in 18.5%.

Table V indicates the association between gyrA mutations and ciprofloxacin susceptibility phenotypes. Among resistant isolates, 37.2% had double mutations at both codons, while 12.4% had single Ser83 mutations.

Table V
Association of gyrA gene mutation and ciprofloxacin susceptibility of *E. coli* (*n*=113).

Ciprofloxacin susceptibility pattern	Mutations at specific codon		
	Ser83 (n) (%)	Asp87 (n) (%)	Both Ser83 and Asp 87 (n) (%)
Sensitive	5 (4.4%)	0	0
Intermediate	2 (1.8%)	0	0
Resistant	14 (12.4%)	0	42 (37.2%)

Table VI exhibits the specific amino acid substitution patterns with corresponding ciprofloxacin MIC values. Single-site Ser 83 mutations associated with MIC values ranging from 0.25-2 µg/ml, indicating low-level resistance. In contrast, double mutations at both Ser83 and Asp87 exclusively correlated with MICs ≥8 µg/ml, showing high-level resistance.

Table VI
Amino-acid changes in gyrA genes of Escherichia coli and corresponding MIC of Ciprofloxacin (*n*=63).

Substitution site	No. of Isolates	Mutation observed in *E. coli* isolates at specific MIC of ciprofloxacin (µg/ml)						
		0.25	0.5	1	2	4	8	16
Single site mutation 21 (Ser 83)	21	5	2	5	7	2	-	-
Single site mutation (Asp 87)	0	-	-	-	-	-	-	-
Both site mutations (Ser 83 & Asp 87)	42	-	-	-	-	-	19	23

Table VII shows the antibiotic resistance profiles between single-mutated and double-mutated *E. coli* strains. Double-mutated strains were more resistant to a wide array of antibiotic classes, especially the fluoroquinolone class: 100% ciprofloxacin-resistant versus 76.2% in single mutants; and nalidixic acid, 100% versus 90.5%. Resistance patterns of non-fluoroquinolone antibiotic classes, however, remained largely unchanged, indicating that they may depend on distinct mechanisms of resistance.

Table VII
Comparison of antibiotic resistance between single-mutated and double-mutated Escherichia coli strains (*n*=63).

Antimicrobial Agents	Single-strain mutation (n=21)	Double-mutated strains (n=42)
Mecillinam (10 µg)	15 (71.4%)	28 (66.7%)
Ceftazidime (30µg)	19 (90.5%)	40 (95.2%)
Cefuroxime (30µg)	18 (85.7%)	40 (95.2%)
Ceftriaxone (30µg)	19 (90.5%)	39 (92.9%)
Cefixime (5µg)	20 (95.2%)	39 (92.9%)
Nalidixic Acid (30µg)	19 (90.5%)	42 (100%)
Ciprofloxacin (5µg)	16 (76.2%)	42 (100%)
Levofloxacin (5µg)	14 (66.7%)	12 (28.6%)
Nitrofurantoin (300µg)	8 (38.1%)	17 (40.5%)
Gentamicin (10µg)	11 52.4%)	17 (40.5%)
Amikacin (30µg)	4 (19%)	11 (26.2%)
Co-trimoxazole (1.25/23.75µg)	20 (95.2%)	41 (97.6%)
Amoxiclav (20/10µg)	17 (81%)	38 (90.5%)
Meropenem (10µg)	3 (14.3%)	5 (11.9%)
Imepenem (10µg)	4 (19%)	9 (21.4%)
Aztreonam (30µg)	18 (85.7%)	41 (97.6%)

Table VIII summarizes the ciprofloxacin susceptibility of different genetic backgrounds. Mutated strains showed 49.5% resistance, compared with only 1.7% resistance among strains without mutations, making the gyrA mutation the major prevailing resistance mechanism. Additionally, double mutations presented total resistance at 100%, while single mutations demonstrated partial penetrance with 66.7% resistance, exemplifying the incremental nature of mutation-mediated resistance. These data highlight the predictive value of genotypic characterization.

Table VIII
Comparative Analysis of Ciprofloxacin Susceptibility Patterns Between Mutated vs Non-Mutated Strains, Single vs Double gyrA mutations, and overall gyrA mutation status in Escherichia coli (*n*=113).

Variable	Category	Ciprofloxacin susceptibility pattern		
		Susceptible n (%)	Intermediate n (%)	Resistant n (%)
E. coli strains	Mutated	5 (4.4%)	2 (1.7%)	56 (49.5%)
	Non mutated	47 (41.6%)	2 (1.7%)	1 (0.8%)
E. coli strains	Single Mutation (n=21)	5 (23.8%)	2 (1.7%)	14 (66.7%)
	Double Mutation (n=42)	0	0	42 (100%)
	-	**Sensitive**		**Resistant**
gyrA gene mutation	Present (n=63)	5 (7.9%)		58 (92.1%)
	Absent (n=50)	47 (94%)		3 (6%)

DISCUSSION

This study provides a comprehensive overview of the dynamics of antimicrobial resistance and fluoroquinolone resistance mechanisms among urinary *E. coli* isolates in Bangladesh and uncovers their resistance patterns. The study confirms *E. coli* as the predominant uropathogen, constituting 81.8% of culture-positive urinary tract infections, which is consistent with Khanal et al. [19]. However, the antibiogram shows a disturbingly high level of resistance among isolates. High levels of resistance to nalidixic acid (72.6%), cefuroxime (67.3%), and ciprofloxacin (52.2%) are consistent with Ruiz et al. and Sahm et al. [20,21]. These contrasts reveal the differential global evolution of antimicrobial resistance shaped by patterns of antibiotic consumption, regulatory oversight, and healthcare infrastructure. These molecular data led chromosomal mutations as the main driver of fluoroquinolone resistance, with mutations of gyrA present in 55.7% of the tested isolates. This prevalence contrasts the situation reported by Hoseinzadeh et al., where plasmid-mediated quinolone resistance determinants stand for a significant percentage of the resistance phenotypes [22]. Particularly noteworthy is the preponderance of double mutants involving Ser83 and Asp87 (37.1% of mutated isolates), a hallmark of high-level resistance and clinical failure. Azargun et al. reported similar identified Ser83Leu and Asp87Asn as the two most common changes in the Iranian population, further emphasizing a geographical spreading of mutation patterns carrying pivotal therapeutic consequences [23]. The strong genotype-phenotype correlation depicted here, where 92.1% of mutated isolates turned out as resistant, underlines very well the predictive value of molecular markers. The overt linkage of double mutants to MIC values of at least 8 µg/ml further illustrates the stepwise acquisition of mutations as resistance progresses, a process well described in in vitro selections and clinical isolates [24]. The lack of isolates with only Asp87 mutations further supports the idea that Ser83 changes are often the first evolutionary event, due to particularly favorable fitness dynamics. The study also shows meaningful concordance between disc diffusion and MIC methods, supporting continued use of disc diffusion in routine diagnostic workflows, while recognizing the higher precision of MIC testing for pharmacokinetic-pharmacodynamic

optimization and more nuanced clinical decision-making [25]. The observed bimodal MIC distribution underlines genetic segmentation between wild-type populations and mutated resistant strains. Cross-resistance patterns further complicate clinical management. Indeed, ciprofloxacin-resistant isolates often showed resistance to β-lactams and trimethoprim-sulfamethoxazole, reflecting selective pressure that co-favors multidrug resistance pathways shaped by antibiotic overuse and horizontal gene transfer [26]. Notably, carbapenems remained highly effective, with resistance below 10%, consistent with global evidence supporting their standing as last-line agents [27]. Aminoglycosides and nitrofurantoin also maintained considerable activity and, hence, can continue to play a role as therapeutic alternatives in fluoroquinolone-resistant infections. Clinically and programmatically, these findings support reconsideration of empirical fluoroquinolone therapy in settings with similar resistance landscapes. Local susceptibility patterns need to be incorporated into the treatment algorithms, and rapid molecular diagnostics targeting gyrA mutations may enable early therapeutic precision with reduced unnecessary antibiotic exposure [28]. From the broader public health perspective, the findings shed light on systemic gaps in antimicrobial stewardship, regulatory control, diagnostic capacity, and community-level education that perpetuate the high burden of resistance [29]. The decreasing usefulness of existing antibiotics also highlights the need to examine new therapeutics, such as phage therapy and immunomodulatory strategies [30].

LIMITATIONS

Because of the cross-sectional design, temporal trends in resistance evolution could not be assessed, and other possible resistance mechanisms were not investigated, including parC mutations, efflux pump expression, and plasmid-mediated quinolone resistance genes.

CONCLUSION

This study detected alarmingly high rates of fluoroquinolone resistance among urinary *E. coli* isolates, which were mainly due to double mutations in codons 83 and 87 within the gyrA gene. A strong genotype-phenotype correlation establishes molecular screening as a useful tool for predicting resistance patterns. Extensive multidrug resistance warrants re-evaluation of empirical treatment policies and determines the crucial role of an antimicrobial stewardship program. These results reiterate the importance of continuing surveillance and molecular characterization to support rational antibiotic policies in combating the growing menace of antimicrobial resistance.

RECOMMENDATIONS

Whole-genome sequencing approaches should be used to comprehensively characterize all resistance mechanisms and clonal relationships among resistant strains in future studies. Multicenter longitudinal surveillance with diverse patient populations and healthcare settings should, therefore, provide more representative national resistance data.

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