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ISSN: 2663-9491 e-ISSN: 2789-6897

ORIGINAL ARTICLE

Occurrence of gyrA Gene Mutations and their Association with Ciprofloxacin MIC Levels among Uropathogenic *Escherichia coli* Isolates

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Received: 24 July 2026
Accepted: 27 July 2026
Published Online: 29 July 2026

Published by:
Gopalganj Medical College, Gopalganj, Bangladesh

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DOI: 10.5281/zenodo.21786209

ABSTRACT

Introduction: *Uropathogenic Escherichia coli is the leading cause of urinary tract infection, while increasing ciprofloxacin resistance has reduced the effectiveness of empirical therapy. Mutations in the gyrA gene, especially at Ser83 and Asp87, are important mechanisms of fluoroquinolone resistance and may increase ciprofloxacin minimum inhibitory concentration (MIC).* ***Methods & Materials & Materials:*** *This cross-sectional analytical study aimed to determine the prevalence of gyrA mutations among uropathogenic E. coli isolates and assess their association with ciprofloxacin MICs. The study was conducted at the Department of Microbiology, Sir Salimullah Medical College, Dhaka, from January to December 2020. A total of 229 urine samples from clinically suspected UTI patients were cultured, and 113 uropathogenic E. coli isolates were analyzed. Antimicrobial susceptibility was tested by Kirby-Bauer disc diffusion, ciprofloxacin MIC was determined by agar dilution following CLSI 2019 breakpoints, and gyrA mutations at Ser83 and Asp87 were detected by PCR-RFLP.* ***Result:*** *Among culture-positive isolates, E. coli was predominant (113, 81.88%). Ciprofloxacin MICs ranged from 0.007 to 16 µg/mL; 52 (46.02%) isolates were sensitive, 4 (3.54%) intermediate, and 57 (50.44%) resistant. The gyrA gene was detected in all isolates, with mutations in 63 (55.75%). A single Ser83 mutation was found in 21 (18.58%), while double Ser83 and Asp87 mutations were found in 42 (37.17%).* ***Conclusion:*** *The gyrA gene mutations were common among uropathogenic E. coli and were significantly associated with ciprofloxacin resistance and elevated MIC levels. Double mutations at Ser83 and Asp87 were strongly associated with high MIC values, indicating the need for culture-guided, cautious use of ciprofloxacin in UTI treatment.*

Keywords: *Uropathogenic Escherichia coli, gyrA gene mutation, Ciprofloxacin resistance and Urinary tract infection*

(The Insight 2026; 9(3): 560-564)

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INTRODUCTION

Urinary tract infection (UTI) is among the most frequent bacterial infections encountered in both community and hospital practice, causing substantial morbidity, repeated health-care visits, antibiotic exposure, and economic burden. Uropathogenic *Escherichia coli* (UPEC) remains the dominant etiological agent because of its ability to colonize the periurethral region, adhere to uroepithelial cells, form intracellular bacterial communities, and persist despite host defense mechanisms [1]. Globally, UTIs are especially common among women, with an estimated lifetime incidence of 50-60%, and recurrent episodes are frequent [2]. Although many UTIs are initially managed empirically, increasing antimicrobial resistance has reduced the reliability of standard oral agents and has made culture-guided treatment increasingly important [3]. Fluoroquinolones, particularly ciprofloxacin, have long been used for UTI treatment because of high oral bioavailability, good urinary penetration, and activity against Gram-negative bacilli. However, global evidence shows a sustained rise in ciprofloxacin-resistant *E. coli*. Systematic reviews have reported high resistance rates in both community- and hospital-acquired *E. coli* UTIs, with greater resistance burdens in regions with weaker antibiotic regulation and stewardship [4,5]. Resistance to fluoroquinolones in uncomplicated community-acquired UTIs has also become sufficiently common in many countries to limit their empirical use [6]. In South Asia and Bangladesh, the situation is especially concerning because unrestricted antibiotic access, self-medication, incomplete courses, and limited routine susceptibility surveillance contribute to antimicrobial selection pressure [7]. Recent Bangladeshi studies have repeatedly identified *E. coli* as the leading uropathogen and documented increasing resistance to commonly used agents, including ciprofloxacin [8,9]. The clinical relevance of ciprofloxacin resistance extends beyond laboratory reporting. Resistant UPEC may lead to treatment failure, prolonged symptoms,

ISSN: 2663-9491 e-ISSN: 2789-6897

recurrence, pyelonephritis, hospitalization, and use of broader-spectrum reserve antibiotics. At the molecular level, ciprofloxacin primarily inhibits bacterial DNA gyrase and topoisomerase IV. Resistance commonly occurs through point mutations in the quinolone resistance-determining regions of target genes, particularly *gyrA*, and may be compounded by *parC* mutations, plasmid-mediated quinolone resistance genes, and efflux mechanisms [10]. Among these mechanisms, mutations in *gyrA*, especially at codons encoding Ser83 and Asp87, are consistently linked with increased ciprofloxacin minimum inhibitory concentration (MIC) and high-level resistance [11,12]. Quantitative reviews indicate that target-site mutations in *gyrA* and *parC* confer larger MIC increases than many other single resistance mechanisms, and combinations of mutations may produce marked elevations in ciprofloxacin MIC [11]. Therefore, MIC-based phenotyping, when paired with mutation detection, provides more clinically meaningful information than susceptibility categories alone. Despite this biological plausibility, important knowledge gaps remain. Many local studies report ciprofloxacin susceptibilities by disc diffusion alone, whereas fewer examine MIC distribution. Even fewer link specific *gyrA* mutation patterns with MIC levels among UPEC isolates. In Bangladesh, molecular studies have described quinolone resistance genes and *gyrA* mutations in UTI pathogens, but there remains a need for focused analysis of UPEC isolates that combines phenotypic MIC data with mutation status [13]. Such evidence can improve local understanding of resistance mechanisms, support rational empirical therapy, and guide future surveillance strategies. Therefore, the present study aimed to determine the occurrence of *gyrA* gene mutations among uropathogenic *E. coli* isolates and to evaluate their association with ciprofloxacin MIC levels.

METHODS & MATERIALS

This cross-sectional analytical study was conducted in the Department of Microbiology, Sir Salimullah Medical College, Dhaka, from January 2020 to December 2020. Patients clinically suspected of having a urinary tract infection who attended the inpatient or outpatient departments and submitted urine samples for culture and sensitivity testing were included. Patients who had taken antibiotics within the previous 14 days, were receiving current antibiotic therapy, or provided catheterized urine samples were excluded. A total of 229 urine samples were collected following standard aseptic procedures. Urine samples were cultured on MacConkey agar and blood agar, incubated aerobically at 37°C for 24 hours. Bacterial isolates were identified by colony morphology, Gram staining, and standard biochemical tests, including Kligler iron agar, motility, indole urea, citrate utilization, and oxidase tests. Among culture-positive samples, 113 uropathogenic Escherichia coli isolates were selected for further analysis. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar, according to the Clinical and Laboratory Standards Institute guidelines (2019). The minimum inhibitory concentration (MIC) of ciprofloxacin was determined by the agar dilution method using concentrations ranging from 0.007 µg/mL to 16 µg/mL. MIC interpretation followed CLSI 2019 breakpoints: sensitive ≤0.25 µg/mL, intermediate 0.5 µg/mL, and resistant ≥1 µg/mL. For analytical comparison, intermediate isolates were considered resistant. Detection of gyrA gene mutations was performed by polymerase chain reaction-restriction fragment length polymorphism, PCR-RFLP. DNA was extracted from overnight growth of E. coli. A 164-bp fragment of the gyrA gene spanning the Ser83 and Asp87 codons was amplified, followed by digestion with the HinfI restriction enzyme. Digested products were separated by agarose gel electrophoresis and interpreted based on band patterns. Data were analyzed using appropriate statistical methods using SPSS (version 26.0). Categorical variables were expressed as frequency and percentage. Association between gyrA mutation and ciprofloxacin MIC/susceptibility was assessed using a chi-square test, and $p<0.05$ was considered statistically significant.

RESULTS

Table I shows that of 229 urine samples, 138 (60.26%) yielded bacterial growth. Among the culture-positive isolates, *Escherichia coli* was the predominant organism, accounting for 113 (81.88%), followed by *Klebsiella* spp. (8.70%) and *Pseudomonas* spp. (6.52%).

Table I: Culture yield and distribution of urinary isolates

	Frequency (n)	Percentage (%)
Total urine samples studied	229	100
Culture-positive samples	138	60.26
No growth	91	39.74
Escherichia coli	113	81.88
Klebsiella spp.	12	8.7
Pseudomonas spp.	9	6.52
Citrobacter spp.	2	1.44
Proteus spp.	1	0.72
Staphylococcus aureus	1	0.72

Table II shows that ciprofloxacin MIC values ranged from 0.007 µg/ml to 16 µg/ml. Based on MIC breakpoints, 52 (46.02%) isolates were sensitive, 4 (3.54%) were intermediate, and 57 (50.44%) were resistant. The highest number of isolates had MIC values of 16 µg/ml (20.35%) and 8 µg/ml (16.81%), followed by 23 µg/ml (19%).

ISSN: 2663-9491 e-ISSN: 2789-6897

Table II: Distribution of ciprofloxacin MIC levels among uropathogenic Escherichia coli isolates

Ciprofloxacin MIC (µg/ml)	Frequency (n)	Percentage (%)	Interpretation
0.007	9	7.96	Sensitive
0.015	11	9.73	Sensitive
0.03	6	5.31	Sensitive
0.06	6	5.31	Sensitive
0.12	9	7.96	Sensitive
0.25	11	9.73	Sensitive
0.5	4	3.54	Intermediate
1	2	1.77	Resistant
2	6	5.31	Resistant
4	7	6.19	Resistant
8	19	16.81	Resistant
16	23	20.35	Resistant

Table III shows that the *gyrA* gene was present in all 113 (100.00%) *E. coli* isolates. Mutation of the *gyrA* gene was detected in 63 (55.75%) isolates, while 50 (44.25%) had no mutation. Among all isolates, 21 (18.58%) had a single Ser83 mutation, and 42 (37.17%) had a double mutation involving both Ser83 and Asp87.

Table III: Distribution and pattern of gyrA gene mutations among uropathogenic Escherichia coli isolates

gyrA gene finding	Frequency (n)	Percentage (%)
gyrA gene present	113	100
gyrA mutation present	63	55.75
gyrA mutation absent	50	44.25
Single mutation (Ser83)	21	18.58
Single mutation (Asp87)	0	0
Double mutation (Ser83 and Asp87)	42	37.17

Table IV shows that among 57 ciprofloxacin-resistant isolates, 42 (73.69%) had a double mutation at Ser83 and Asp87, while 14 (24.56%) had a single mutation at Ser83. Among 52 ciprofloxacin-sensitive isolates, 47 (90.38%) had no *gyrA* mutation. No isolate showed the Asp87 mutation.

Table IV: Association between gyrA gene mutation and ciprofloxacin susceptibility

Ciprofloxacin susceptibility pattern	Ser83	Asp87	Both Ser83 & Asp87	No mutation
	n (%)			
Sensitive (n=52)	5 (9.62)	0 (0.00)	0 (0.00)	47 (90.38)
Intermediate (n=4)	2 (50.00)	0 (0.00)	0 (0.00)	2 (50.00)
Resistant (n=57)	14 (24.56)	0 (0.00)	42 (73.69)	1 (1.75)
Total	21 (18.58)	0 (0.00)	42 (37.17)	50 (44.25)

Table V shows a significant association between the *gyrA* mutation and ciprofloxacin resistance ($p<0.05$). Among 63 mutated isolates, 58 were ciprofloxacin-resistant, whereas only 5 were sensitive. In contrast, among 50 non-mutated isolates, 47 were sensitive, and only 3 were resistant.

Table V: Binary association between gyrA mutation status and ciprofloxacin resistance

gyrA mutation status	Ciprofloxacin sensitive	Ciprofloxacin resistant	Total	p-value
	n (%)			
Mutation present	5 (7.94)	58 (92.06)	63 (100.00)	p<0.05
Mutation absent	47 (94.00)	3 (6.00)	50 (100.00)	
Total	52 (46.02)	61 (53.98)	113 (100.00)	

Table VI shows that the single Ser83 mutation was observed mainly at lower to moderate MIC levels, ranging from 0.25 µg/ml to 4 µg/ml. In contrast, all 42 isolates with double mutations at Ser83 and Asp87 had high MICs, with 19 at 8 µg/ml and 23 at 16 µg/ml, indicating that double mutation was strongly associated with higher ciprofloxacin MICs.

ISSN: 2663-9491 e-ISSN: 2789-6897

Table VI: Distribution of gyrA mutation types according to ciprofloxacin MIC level

Mutation type	No. of isolates	0.25	0.5	1	2	4	8	16
Single mutation (Ser83)	21	5	2	5	7	2	0	0
Single mutation (Asp87)	0	0	0	0	0	0	0	0
Double mutation (Ser83 and Asp87)	42	0	0	0	0	0	19	23
Total mutated isolates	63	5	2	5	7	2	19	23

DISCUSSION

The present study demonstrated a high burden of ciprofloxacin resistance and *gyrA* gene mutation among uropathogenic *Escherichia coli* isolates. Of 229 urine samples, bacterial growth was detected in 138 (60.26%), and *E. coli* was the predominant isolate, accounting for 113 (81.88%) of culture-positive cases. This finding confirms UPEC's major role as the leading bacterial cause of UTI and is consistent with previous reports from Bangladesh and other countries, where *E. coli* has remained the most frequent uropathogen [7-9,14]. However, the proportion of *E. coli* in the present study was slightly higher than in some Bangladeshi studies, which reported *E. coli* in approximately 49% to 62% of UTI cases [7,8,14]. This variation may be related to differences in patient selection, hospital setting, exclusion criteria, prior antibiotic exposure, and local microbiological ecology. Ciprofloxacin resistance was also considerable in this study. By agar dilution MIC, 57 isolates (50.44%) were resistant, and 4 (3.54%) were intermediate. When intermediate isolates were considered resistant, overall ciprofloxacin non-susceptibility was 61 (53.98%). This result is close to the findings of Acherjya et al., who reported 57.3% ciprofloxacin resistance among urinary *E. coli* isolates in Bangladesh [15], and Nobel et al., who found 59.6% resistance in Mymensingh [16]. Mahjabin et al. also reported a comparable resistance rate of 55% among *E. coli* isolates from complicated UTI cases in Dhaka [14]. In contrast, Haque et al. reported a higher ciprofloxacin resistance rate of 71% among UTI pathogens in Bangladesh, while Das et al. found 83.6% ciprofloxacin resistance among *E. coli* in a One Health study [13,17]. The comparatively lower rate in the present study may reflect differences in the study population and the inclusion of only urine-derived *E. coli* isolates. Compared with global data, the resistance rate in this study was relatively high. Fasugba et al. reported pooled ciprofloxacin resistance rates of 27% in community-acquired and 38% in hospital-acquired *E. coli* UTI [4]. Bryce et al. found ciprofloxacin resistance of 26.8% among paediatric *E. coli* UTI isolates in non-OECD countries , while Stapleton et al. reported variable fluoroquinolone resistance in community-acquired uncomplicated UTI, with higher rates in Asia [5,6]. The higher resistance observed in the current study may be explained by frequent empirical fluoroquinolone use, over-the-counter access to antibiotics, incomplete treatment courses, and weak antimicrobial stewardship in many low- and middle-income settings. The molecular findings further explain the observed resistance pattern. The *gyrA* gene was present in all 113 *E. coli* isolates, and a *gyrA* mutation was detected in 63 (55.75%). Among mutated isolates, 21 (33.33%) had a single Ser83 mutation, and 42 (66.67%) had a double mutation involving Ser83 and Asp87. Mutation was significantly associated with ciprofloxacin resistance ($p<0.05$). Among 63 mutated isolates, 58 were ciprofloxacin non-susceptible, whereas among 50 non-mutated isolates, 47 were ciprofloxacin sensitive. Similar findings were reported by Esmaeel et al., who detected *gyrA* mutations in 76.7% of fluoroquinolone-resistant UPEC isolates [18]. El-Mahdy et al. found a double Ser83/Asp87 mutation in 69.4% of ciprofloxacin-resistant isolates, while Neyestani et al. reported a *gyrA* mutation in 81.81% of resistant *E. coli*, mostly a double Ser83Leu/Asp87Asn mutation (78.78%) [19,20]. These studies support the present finding that the *gyrA* mutation, particularly the double mutation, is a key mechanism of ciprofloxacin resistance. The relationship between mutation type and MIC level was clinically important. In this study, a single Ser83 mutation was observed at lower to moderate MIC levels (0.25-4 µg/ml), whereas all double-mutated isolates had high MIC values: 19 at 8 µg/ml and 23 at 16 µg/ml. This indicates that the double mutation was strongly associated with a higher ciprofloxacin MIC. Ghadiri et al. similarly found that multiple topoisomerase mutations were significantly associated with increased ciprofloxacin MIC ($p=0.001$) [21]. Chegene Lorestani et al. reported very high MIC50 and MIC90 values of 64 and 256 µg/mL, respectively, among ESB L-producing urinary *E. coli* with topoisomerase mutations [22]. Tewawong et al. also observed that high-level ciprofloxacin-resistant *E. coli* commonly carried double GyrA mutations at codons 83 and 87 [23]. A systematic review by van der Putten et al. confirmed that *gyrA* and *parC* mutations contribute substantially to ciprofloxacin MIC elevation [11]. Some discordant findings were observed. Five ciprofloxacin-sensitive isolates carried the Ser83 mutation, while three non-mutated isolates were non-susceptible. This suggests that the *gyrA* mutation alone may not fully explain ciprofloxacin resistance or susceptibility. Other mechanisms, such as *parC* mutation, plasmid-mediated quinolone resistance genes, and efflux pump overexpression, may contribute [12,13,20,].

LIMITATIONS

This was a single-center study with a relatively small sample size. Only gyrA mutations at Ser83 and Asp87 were assessed, while other resistance mechanisms, such as parC mutations, plasmid-mediated quinolone resistance genes, and efflux pump activity, were not evaluated.

CONCLUSION

This study concluded that the *gyrA* gene mutation was common among uropathogenic *Escherichia coli* isolates and was significantly associated with ciprofloxacin resistance and higher MIC levels. The double mutation involving Ser83 and Asp87 was the predominant mutation pattern and was strongly associated with high ciprofloxacin MIC values. These findings suggest that ciprofloxacin should be used cautiously for UTI treatment, preferably guided by culture and susceptibility testing.

RECOMMENDATIONS

Routine culture and antimicrobial susceptibility testing should be performed before prescribing ciprofloxacin for urinary tract infection. Molecular surveillance of *gyrA* and other quinolone resistance genes should be strengthened to monitor the emergence of fluoroquinolone resistance. Further multicenter studies with larger sample sizes are recommended to evaluate additional mechanisms, including *parC* mutations, plasmid-mediated quinolone resistance genes, and efflux pump activity.

FUNDING

No funding sources

CONFLICT OF INTEREST
None declared

ETHICAL APPROVAL
The study was approved by the Institutional Ethics Committee.

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