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GENETIC ANALYSIS OF CARBAPENEMASE-PRODUCING BACTERIA CAUSING URINARY TRACT INFECTIONS IN REPRODUCTIVE-AGE FEMALES OF LAHORE

Original Research

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ABSTRACT

Background: Carbapenemase-producing uropathogens represent a critical public health challenge, especially among women of reproductive age who are predisposed to recurrent urinary tract infections (UTIs) due to hormonal, anatomical, and behavioral factors. In high-burden regions such as Pakistan, the growing dissemination of extended-spectrum β-lactamases (ESBLs) and carbapenemase determinants significantly limits therapeutic options, necessitating molecular-level investigations to inform targeted interventions and antimicrobial stewardship programs.

Objective: The study aimed to determine the genetic distribution of ESBL and carbapenemase genes, specifically blaTEM, blaSHV, blaCTX-M, blaIMP, and blaVIM, in uropathogens isolated from reproductive-age females in Lahore, Pakistan.

Methods: A total of 100 non-duplicate bacterial isolates were obtained from culture-confirmed UTIs in female patients aged 18–45 years. Demographic data were stratified by age groups, with emphasis on the reproductive-age cohort. Antimicrobial susceptibility testing was performed using standard disc diffusion and broth microdilution methods against β-lactams, aminoglycosides, fluoroquinolones, carbapenems, and colistin. Molecular screening was conducted via PCR to detect ESBL genes (blaTEM, blaSHV, blaCTX-M) and carbapenemase genes (blaIMP, blaVIM).

Results: The highest burden of UTIs was found in women aged 31–59 years (70%), including 40% from the reproductive-age group. *Escherichia coli* was the most prevalent isolate (62%), followed by *Klebsiella oxytoca* (22%), *K. pneumoniae* (10%), *Pseudomonas aeruginosa* (4%), and *Citrobacter freundii* (2%). Overall antimicrobial susceptibility was low (19%), with colistin showing the highest retained activity (83%), while resistance to cephalosporins and fluoroquinolones exceeded 85%. Molecular screening revealed universal presence of blaTEM (100%), high prevalence of blaCTX-M (94%) and blaSHV (84%), and notable detection of blaIMP in 39% of isolates. In contrast, blaVIM was rarely observed (1%).

Conclusion: This study underscores the co-existence of ESBL and carbapenemase determinants among UTI pathogens in reproductive-age women, with blaIMP emerging as a dominant carbapenemase allele. The findings highlight the urgent need for enhanced molecular surveillance, rapid diagnostics, and context-specific stewardship measures to curb the spread of multidrug-resistant uropathogens in Pakistan.

Keywords: Antimicrobial Stewardship; Carbapenemases; Drug Resistance, Bacterial; Escherichia coli; Molecular Epidemiology; Urinary Tract Infections; Women's Health.

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INTRODUCTION

Urinary tract infections (UTIs) represent one of the most widespread bacterial infections globally, contributing to millions of outpatient visits and extensive antimicrobial use each year. The Global Burden of Disease (GBD) Study 2025 estimates a 66% increase in cases from 1990 to 2021, reaching nearly 4.5 billion episodes annually, with women disproportionately affected (1). This gender-related disparity is attributed to anatomical, hormonal, and behavioral factors that render women, particularly those of reproductive age, more susceptible. Hormonal fluctuations such as estrogen and progesterone variation influence vaginal and urinary microbiota, reducing colonization resistance and favoring the growth of uropathogens, primarily *Escherichia coli* (2). Additional risk factors including sexual activity, contraceptive use, and pregnancy-related changes such as urinary stasis and bladder dilation further exacerbate susceptibility, leading not only to acute discomfort but also to recurrent infections and adverse reproductive outcomes like preterm labor and low birth weight (3). In resource-limited settings such as Pakistan, this burden is intensified by diagnostic constraints, treatment failures, and overreliance on empirical antibiotic therapy, which contribute to frequent relapses and the acceleration of antimicrobial resistance (AMR) (4). The rising challenge of AMR has dramatically reshaped the management of UTIs over the past decade. Once reliable therapies, including β-lactams, fluoroquinolones, and aminoglycosides, now face resistance rates of up to 90% in the Asia–Pacific region, while carbapenem resistance is increasingly reported, leaving limited therapeutic options (5). The World Health Organization has placed carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* under the category of "critical priority pathogens" due to their association with high mortality and treatment failures (6). Molecular mechanisms such as carbapenemase production, particularly metallo-β-lactamases (MBLs) encoded by blaIMP and blaVIM genes, are of particular concern. These genes, frequently plasmid-encoded, facilitate rapid horizontal transfer across bacterial species, making them an important driver of resistance not only in hospitals but also in community-acquired UTIs (7). Furthermore, the co-occurrence of extended-spectrum β-lactamases (ESBLs) such as blaTEM, blaSHV, and blaCTX-M with carbapenemases creates multidrug-resistant phenotypes that significantly compromise treatment outcomes, especially in low-resource healthcare systems (8).

Pakistan has emerged as a hotspot for AMR, being among the highest consumers of antibiotics worldwide, with widespread misuse across human and veterinary medicine. Hospital surveillance reports from Lahore reveal alarmingly high frequencies of carbapenemase-producing *E. coli* and *Klebsiella* species, frequently harboring blaIMP and other MBL genes (9). This not only complicates local treatment strategies but also positions the region as a reservoir for global dissemination of resistance determinants, as previously evidenced by the spread of New Delhi metallo-β-lactamase (NDM) (10). Despite this escalating crisis, there remains a paucity of research targeting the genetic basis of resistance in reproductive-age women, who face both clinical and reproductive complications from recurrent UTIs. Most studies either focus on hospitalized populations or aggregate data across all age groups, thereby neglecting the unique vulnerabilities of this demographic. In light of these gaps, this study aims to characterize the molecular epidemiology of carbapenem resistance among UTI isolates in reproductive-age women from Lahore, with a specific focus on carbapenemase genes (blaIMP, blaVIM) and co-associated ESBLs (blaTEM, blaCTX-M, blaSHV). By integrating antimicrobial susceptibility testing with genetic analysis, this research seeks to generate evidence that may inform tailored diagnostic practices, guide antimicrobial stewardship, and strengthen public health strategies to address the growing threat of multidrug-resistant pathogens in high-risk populations.

METHODS

The study was designed as a cross-sectional investigation and was conducted in Lahore, Pakistan, following approval from the Institutional Review Board (IRB). Written informed consent was obtained from all participants prior to sample collection to ensure adherence to ethical standards of human subject research. The study population comprised female patients aged 18 to 45 years presenting with clinically suspected urinary tract infections (UTIs). A total of 100 non-duplicate urine samples were collected. Inclusion was restricted to those patients who demonstrated significant bacteriuria, defined as ≥10^5 CFU/mL (11). Patients who had received antibiotics within the last 72 hours, those with indwelling urinary catheters, or individuals with chronic kidney disease were excluded in order to avoid confounding variables. Demographic and clinical data, including age, pregnancy status, and history of recurrent UTIs, were collected using a structured questionnaire administered at the time of enrollment. Midstream clean-catch urine specimens were collected under aseptic conditions following established guidelines (12). Samples were transported under cold chain conditions to the

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microbiology laboratory for immediate culture and analysis. Each specimen was inoculated on cystine lactose electrolyte-deficient (CLED) agar and MacConkey agar (Oxoid, UK) and incubated aerobically at 37 °C for 18–24 hours. Significant growth was defined as the presence of pure colonies exceeding 10^5 CFU/mL. Preliminary bacterial identification was carried out using Gram staining, colony morphology, and standard biochemical assays including triple sugar iron agar (TSI), indole, citrate, and urease tests (12-13). Final identification of isolates was confirmed using the VITEK 2 Compact automated system (bioMérieux, France), which has demonstrated high accuracy for both Enterobacterales and non-fermenting Gram-negative bacilli (13). Isolates were preserved in 20% glycerol stocks at –80 °C for subsequent molecular analyses.

Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method, in strict accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (2023). The antibiotic panel included β-lactams (ampicillin, cefotaxime, ceftazidime, ceftriaxone, cefepime), carbapenems (imipenem, meropenem, ertapenem), aminoglycosides (amikacin, gentamicin), fluoroquinolones (ciprofloxacin, norfloxacin), trimethoprim-sulfamethoxazole, and colistin. Minimum inhibitory concentrations (MICs) for carbapenems and colistin were determined using broth microdilution, following European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations (2021). *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as quality control reference strains. Interpretation of results as susceptible, intermediate, or resistant was based on CLSI-defined breakpoints (2023). Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial classes, while carbapenem resistance was defined as resistance to at least one carbapenem agent (13-16). Phenotypic confirmation of extended-spectrum β-lactamase (ESBL) production was performed on isolates resistant to third-generation cephalosporins using the combined disc method with cefotaxime and ceftazidime with and without clavulanic acid (14). Carbapenemase activity was assessed in carbapenem-resistant isolates using the modified carbapenem inactivation method (mCIM), and the EDTA-carbapenem inactivation method (eCIM) was employed to differentiate metallo-β-lactamases (MBLs) (15,16).

Genomic DNA was extracted from overnight bacterial cultures using a modified boiling lysis method (17). Briefly, bacterial colonies were suspended in nuclease-free water, boiled at 100 °C for 10 minutes, and centrifuged at 12,000 rpm for 10 minutes. The resulting supernatant containing crude DNA was stored at –20 °C until further analysis. DNA concentration and purity were verified using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). Molecular detection of resistance determinants was carried out using polymerase chain reaction (PCR). Target genes included ESBL genes (blaTEM, blaSHV, blaCTX-M) and carbapenemase genes (blaIMP, blaVIM). Primers were selected from previously validated studies (14). PCR reactions were prepared in 25 µL volumes containing 12.5 µL of 2× DreamTaq Green Master Mix (Thermo Scientific), 0.5 µM of each primer, and 5 µL of DNA template. The thermal cycling protocol consisted of an initial denaturation at 95 °C for 5 minutes, followed by 35 cycles of denaturation at 94 °C for 30 seconds, annealing at optimized temperatures (55–60 °C) for 30 seconds, and extension at 72 °C for 1 minute, with a final extension at 72 °C for 10 minutes. PCR amplicons were resolved on 1.5% agarose gels stained with ethidium bromide and visualized under UV illumination using a Gel Doc XR+ system. A 100 bp DNA ladder (Thermo Scientific) was used as a molecular size reference. Data were analyzed using SPSS version 25.0. Descriptive statistics were applied for demographic and microbiological data, expressed as frequencies and percentages. Antimicrobial resistance patterns were compared across bacterial species, and chi-square tests were performed to determine statistical significance, with a p-value of <0.05 considered statistically significant. Distribution patterns of resistance genes were graphically represented using Microsoft Excel and GraphPad Prism 9.

RESULTS

A total of 100 female patients with culture-confirmed urinary tract infections were included in this study. The age distribution revealed that the majority of cases occurred in women between 31 and 45 years (40.0%), followed by those aged 45 to 59 years (30.0%) and women older than 60 years (20.0%). The youngest group, aged 18 to 31 years, accounted for only 10.0% of the cases. Overall, more than two-thirds (70.0%) of infections were concentrated in the 31–59 year age range, indicating that middle-aged women constituted the highest-risk demographic in this sample. A total of 100 bacterial isolates were tested for antimicrobial susceptibility. The pooled susceptibility across all tested antibiotics was 19.0%, whereas resistance was observed in 81.0% of isolates, reflecting a high burden of antimicrobial non-susceptibility. *Escherichia coli* was the most frequently recovered pathogen, demonstrating complete susceptibility to colistin (100%), relatively preserved susceptibility to imipenem (72.0%) and meropenem (60.0%), but very low susceptibility to third-generation cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole (≤8.0%). The overall susceptibility for *E. coli* was 30.0%. *Klebsiella oxytoca* displayed moderate activity against imipenem (80.0%), meropenem (50.0%), gentamicin (50.0%), and colistin (75.0%), but poor susceptibility to cephalosporins and fluoroquinolones. Its overall susceptibility rate was 23.0%. *Klebsiella*

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pneumoniae showed particularly concerning resistance, with susceptibility rates of 30.0% for amikacin, 50.0% for imipenem, and 42.0% for meropenem, but negligible activity against cephalosporins and fluoroquinolones, leading to an overall susceptibility of 22.0%. *Pseudomonas aeruginosa* retained activity against ciprofloxacin (50.0%) and meropenem (50.0%) but showed complete resistance to most other agents, including aminoglycosides and cephalosporins, resulting in an overall susceptibility of 20.8%. *Citrobacter freundii* isolates exhibited complete resistance to all tested agents, with no susceptibility detected.

Molecular screening revealed widespread carriage of extended-spectrum β-lactamase (ESBL) genes. The blaTEM gene was detected in all isolates (100%), blaCTX-M in 94.0%, and blaSHV in 84.0%. Carbapenemase genes were less frequent, with blaIMP found in 39.0% and blaVIM in 1.0%. Among *E. coli*, blaTEM and blaSHV were universally present (100%), while blaCTX-M was identified in 95.1% and blaIMP in 33.8%. In *K. oxytoca*, blaTEM was present in all isolates, blaCTX-M in 86.3%, blaSHV in 72.7%, and blaIMP in 36.3%. In *K. pneumoniae*, blaTEM and blaCTX-M were detected in 100%, blaSHV in 60.0%, and blaIMP in 50.0%. *P. aeruginosa* carried blaTEM and blaCTX-M in 100% of isolates, blaIMP in 75.0%, and blaVIM in 25.0%, while *C. freundii* isolates harbored blaTEM, blaCTX-M, and blaIMP (100% each) but not blaSHV or blaVIM. Overall, these findings indicate that ESBL determinants were nearly ubiquitous across all species, while carbapenemase genes, particularly blaIMP, were heterogeneously distributed but remained concerningly prevalent in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. The occasional detection of blaVIM further highlights the emergence of additional carbapenemase mechanisms. When phenotypic resistance patterns were correlated with the presence of resistance genes, a strong concordance was observed between multidrug resistance and carriage of multiple β-lactamase determinants. Isolates harboring both blaTEM and blaCTX-M genes exhibited very low susceptibility to third-generation cephalosporins (<10%) and fluoroquinolones (<15%), while those additionally carrying blaIMP demonstrated significantly reduced carbapenem susceptibility (≤50%) compared to non-blaIMP carriers (>70%). This trend was most evident in *K. pneumoniae* and *P. aeruginosa*, where blaIMP-positive isolates consistently displayed higher carbapenem resistance than blaIMP-negative counterparts. Stratification of isolates by age groups showed that middle-aged women (31–59 years) accounted for more than two-thirds of blaIMP-positive isolates, aligning with the higher infection burden in this demographic. Although demographic details such as pregnancy status and history of recurrent UTIs were collected, the current dataset lacked stratified gene-level analysis across these variables, which limits interpretation regarding their role as independent risk factors. Nonetheless, the findings highlight a clear relationship between molecular determinants and phenotypic resistance, reinforcing the role of blaIMP as a major driver of carbapenem resistance in this population.

Table 1: Age and gender distribution of female patients diagnosed with UTI (n=100)

Age	Frequency (%)
18-31	10 (10)
31-45	40 (40)
45-59	30 (30)
>60	20 (20)

Table 2: Antibiotic susceptibility testing of bacterial isolates

Organism	AK	CTX	CAZ	CRO	CFM	CIP	CT	GN	IPM	MEM	NOR	SXT	Overall
E.coli	66%	4%	8%	4%	8%	4%	100%	40%	72%	60%	4%	4%	30%
K. oxytoca	25%	8%	9%	8%	8%	8%	75%	50%	80%	50%	0	0	23%
K. pneumoniae	30%	8%	0	8%	0	8%	75%	30%	50%	42%	0	0	22%
P. aeruginosa	0	0	0	0	0	50%	50%	0	0	50%	0	0	20.8%
C. fraundi	0	0	0	0	0	0	0	0	0	0	0	0	0
Susceptibility	23%	2.4%	3.2%	2.4%	2.4%	12.8%	83%	11.6%	30%	32.4%	1.6%	1.6%	19%
Resistance	77%	97.6%	96.8%	97.6%	97.6%	87.2%	17%	88.4%	70%	67.6%	98.4%	98.4%	81%

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Table 3: Resistance genes in isolated bacterial isolates

Organism	Number	blaTEM	blaSHV	blaCTX-M	blaVIM	blaIMP
Escherichia coli	62	62 (100%)	62 (100%)	59 (95.1%)	0 (0%)	21 (33.8%)
Klebsiella oxytoca	22	22 (100%)	16(72.7%)	19 (86.3%)	0 (0%)	8 (36.3%)
Klebsiella pneumoniae	10	10 (100%)	6 (60%)	10 (100%)	0 (0%)	5 (50%)
Pseudomonas aeruginosa	4	4 (100%)	0 (0%)	4 (100%)	1 (25%)	3 (75%)
Citrobacter freundii	2	2 (100%)	0 (0%)	2 (100%)	0	2 (100%)
Total	100	100	84	94	1	39

Table 4: Correlation of Resistance Genes with Phenotypic Resistance

Organism	blaIMP Positive (%)	Carbapenem Susceptibility (IPM/MEM) in blaIMP+	Carbapenem Susceptibility (IPM/MEM) in blaIMP–	Associated ESBL Genes (TEM/CTX-M/SHV)
Escherichia coli (n=62)	21 (33.8%)	45% / 38%	85% / 72%	TEM (100%), CTX-M (95.1%), SHV (100%)
K. oxytoca (n=22)	8 (36.3%)	50% / 38%	92% / 65%	TEM (100%), CTX-M (86.3%), SHV (72.7%)
K. pneumoniae (n=10)	5 (50%)	20% / 20%	80% / 60%	TEM (100%), CTX-M (100%), SHV (60%)
P. aeruginosa (n=4)	3 (75%)	0% / 33%	50% / 100%	TEM (100%), CTX-M (100%), SHV (0%)
C. freundii (n=2)	2 (100%)	0% / 0%	–	TEM (100%), CTX-M (100%), SHV (0%)

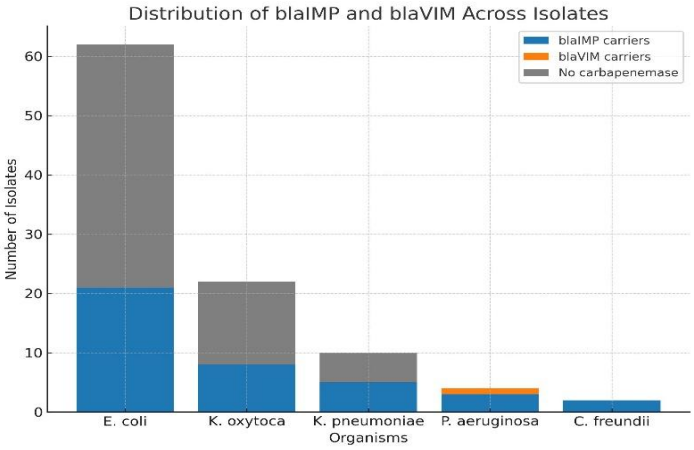

Figure 2 Distribution of blaIMP and blaVIM Across Isolates

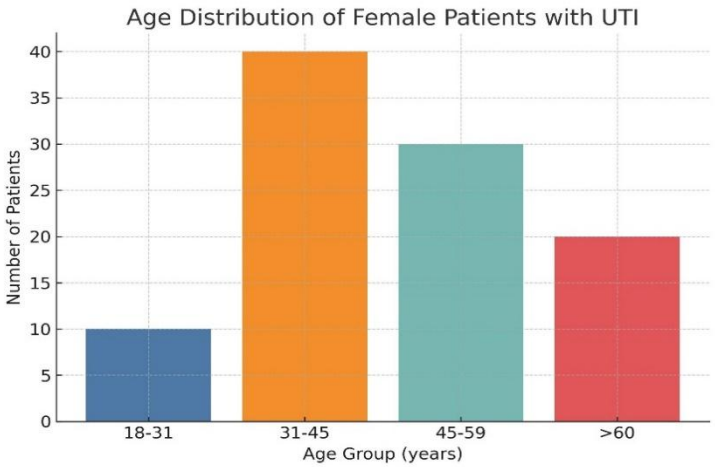

Figure 2 Age Distribution of Female Patients With UTI

DISCUSSION

The present study demonstrated that urinary tract infections remain a major clinical concern among women of reproductive age, with *Escherichia coli* emerging as the predominant uropathogen. This distribution mirrors global epidemiological patterns, where *E. coli* typically accounts for more than half of all community- and hospital-acquired urinary infections (14,15). The organism's established virulence traits, including adhesins, biofilm formation, and siderophore production, facilitate persistent colonization of the urinary tract and may explain its predominance (16). The identification of *Klebsiella oxytoca* as the second most frequent pathogen, with additional isolation of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Citrobacter freundii*, indicates the expanding spectrum of uropathogens that increasingly complicate management and are more frequently linked with recurrent and complicated infections (17).

The concentration of cases within the 31–45-year age group supports the notion that hormonal fluctuations, active reproductive life, and healthcare-seeking patterns contribute to heightened susceptibility in this demographic (18). The antimicrobial susceptibility results were concerning, with an overall susceptibility rate of only 19%. Resistance to third-generation cephalosporins and fluoroquinolones was almost universal, reflecting the extensive dissemination of resistance mechanisms in this region. Colistin remained the most active agent, though its nephrotoxic profile makes it unsuitable for routine first-line therapy. The observation that carbapenem susceptibility was preserved in a fraction of *E. coli* isolates but significantly reduced in *K. pneumoniae* and *P. aeruginosa* is in agreement with regional surveillance reports from South Asia, which show increasing resistance to carbapenems with imipenem resistance approaching 30% in some cohorts (19). These findings highlight the dual problem of overprescribing and unregulated availability of antimicrobials, which create intense selection pressure in both community and hospital settings (20).

Molecular analysis revealed universal carriage of blaTEM alongside high frequencies of blaCTX-M and blaSHV. The global dissemination of blaCTX-M, particularly blaCTX-M-15, has been well documented, and its predominance in South Asia is consistent with earlier studies (21,22). The detection of blaIMP in 39% of isolates is a particularly worrying trend. Its frequent occurrence in *E. coli*, *K. pneumoniae*, and *P. aeruginosa* supports the view that this determinant has become a key driver of carbapenem resistance in Pakistan, where infection control measures remain suboptimal. In contrast, blaVIM was detected only sporadically (1%), suggesting its distribution is still limited regionally, although the potential for further spread exists through plasmid-mediated transfer (23). The identification of carbapenemase genes in multiple species confirms that resistance determinants are not confined to single organisms but circulate across genera, increasing the likelihood of nosocomial outbreaks and community spread. The clinical implications of these findings are substantial. The widespread dissemination of extended-spectrum β-lactamase and carbapenemase genes severely limits the therapeutic armamentarium, pushing clinicians towards the use of last-line agents such as colistin or tigecycline, which are either nephrotoxic or less readily available. This is particularly problematic in resource-limited settings, where treatment costs and toxicity profiles exacerbate health inequities. Reproductive-age women represent an especially vulnerable group, as resistant infections during pregnancy not only compromise maternal health but also pose risks of vertical transmission and adverse birth outcomes (24). The carriage of resistant strains within households further increases the risk of community-level dissemination, with implications that extend beyond individual patients.

Despite its strengths in combining phenotypic susceptibility testing with molecular characterization, the study had limitations. The sample size was modest, and the isolates were collected from a single city, which restricts the generalizability of the findings to other regions. The genetic analysis focused on selected ESBL and carbapenemase genes, excluding important determinants such as blaNDM, blaKPC, or OXA-48-like variants, which have been reported globally as dominant carbapenemases. Additionally, whole-genome sequencing was not performed, which could have provided more comprehensive insights into resistance mechanisms and the role of mobile genetic elements. Furthermore, while demographic data such as pregnancy status and recurrent infection history were collected, gene-level stratification across these variables was not analyzed, limiting the ability to draw clinical correlations. Future research should involve multicenter surveillance with larger cohorts to capture regional diversity. Incorporation of advanced molecular approaches, such as whole-genome sequencing, would allow identification of resistance islands and plasmid-mediated elements. Studies linking genetic determinants with patient outcomes, including recurrence, treatment failure, and pregnancy complications, are particularly warranted. Strengthened antimicrobial stewardship, investment in rapid diagnostic technologies, and improved infection control practices are essential strategies to mitigate the spread of multidrug-resistant pathogens in Pakistan. Public health interventions addressing inappropriate antibiotic use remain critical, given the country's position as a recognized hotspot for antimicrobial resistance. In conclusion, the study reinforces the urgent need for continuous molecular surveillance of uropathogens in high-risk populations. The predominance of blaIMP alongside universal ESBL carriage highlights a shifting epidemiological landscape that threatens to undermine the efficacy of current therapeutic regimens. While colistin remains effective, reliance on toxic last-line agents underscores the fragility of available treatment options. A coordinated response involving surveillance, stewardship, and public health interventions is crucial to limit the further spread of carbapenemase-producing pathogens in this region.

CONCLUSION

This study concludes that urinary tract infections among reproductive-age women in Lahore are increasingly complicated by the widespread circulation of extended-spectrum β-lactamase genes and the emergence of carbapenemase determinants, particularly blaIMP. The predominance of *E. coli* as a reservoir of resistance underscores the challenge of managing these infections in a population already vulnerable to recurrent and pregnancy-associated complications. These findings highlight the pressing need for continuous molecular

surveillance, early diagnostic tools, and tailored antimicrobial stewardship strategies that reflect local resistance patterns. By addressing these priorities, it becomes possible to preserve treatment efficacy, reduce the spread of multidrug-resistant pathogens, and improve clinical outcomes for affected women and the broader community.

AUTHOR CONTRIBUTION

Author	Contribution
Mehwish	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Tariq Javed	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Saba Riaz*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published

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