ORIGINAL ARTICLE

ANNALS OF PUNJAB MEDICAL COLLEGE

Escalating Risk of Rising Antimicrobial Resistance among UroPathogens: A Retrospective Study from a Tertiary Care Hospital in Lahore

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Submitted for Publication: 10-04-2025
Accepted for Publication 18-11-2025

How to Cite: Naqvi M, Nadeem S, Hussain A, Dildar S, Bakhat S, Javed S. Escalating Risk of Rising Antimicrobial Resistance among UroPathogens: A Retrospective Study from a Tertiary Care Hospital in Lahore. APMC 2025;19(4):272-276. **DOI: 10.29054/APMC/2025.1755**

ABSTRACT

Background: Urinary tract infections are common and increasingly complicated by antimicrobial-resistant uropathogens. Monitoring local resistance patterns is essential to guide effective treatment and limit the spread of resistance. **Objective:** To ascertain the frequency of uropathogens and their antimicrobial susceptibility pattern. **Study Design:** Retrospective study. **Settings:** Department of Microbiology at Shalimar Hospital, Lahore Pakistan. **Duration:** January 2024 to June 2024. **Methods:** Midstream urine samples were collected from patients who had symptomatic urinary tract infections. Culture and identification of isolates were done as per standard microbiology procedures. Antibiotic susceptibility was performed according to Clinical and Laboratory Standards Institute guidelines 2024. All Information was obtained from the hospital information management system. **Results:** A total of 349 urine samples were received for culture. Only 146 samples yielded the growth of uropathogens. *Escherichia coli* was the most commonly isolated microorganism, 65.7% (96/146), followed by *Enterococcus spp*, 12.3% (18/146). A low level of resistance has been observed for *E. coli* against meropenem (10%), nitrofurantoin (6%), and Fosfomycin (5%). **Conclusion:** The continuous surge in antimicrobial resistance among uropathogens is frightening, which highlights the significance of monitoring antibiotic susceptibility trends as a key strategy for implementing antimicrobial stewardship.

Keywords: *Antimicrobial resistance, Escherichia coli, Urinary tract infections, Uropathogens.*

INTRODUCTION

Uropathogens are a group of microorganisms leading to urinary tract infections (UTIs), some of the most frequent bacterial infections worldwide, with millions of new cases every year. These pathogens primarily affect the urinary tract, encompassing the kidneys, ureters, bladder, and urethra, and cause diseases ranging from an uncomplicated cystitis (bladder infection) to a potentially serious pyelonephritis (kidney infection).[1] Escherichia coli is the most common cause, accounting for 75% to 90% of cases. Its colonization can occur in the urinary tract due to its virulence factors like fimbriae and toxins.[2] Other frequent bacterial species are *Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, Staphylococcus saprophyticus, and Pseudomonas aeruginosa.*[3] The fungal pathogens, mainly Candida species members, are rare and occur primarily in the immunosuppressed host.[4]

The gender design in UTI epidemiology and risk factors saddles a notably wide design, especially for women, due to anatomical risk characteristics including shorter urethra and known risk component manners such as sexual activity, use of urinary catheters, diabetes, and open urinary obstruction.[5-7] Diagnosis strongly relies on urinalysis and urine culture, as these two tests determine causative agents and enable targeted treatment. However, multidrug-resistant uropathogens with resistance mechanisms such as extended-spectrum beta-lactamase (ESBL) and carbapenemase have become more common, and this jeopardizes the efficacy of

conventional antibiotics and underscores the necessity of novel therapeutic strategies.[6,7]

Understanding the pathogenicity, transmission dynamics, and resistance profiles of uropathogens will be necessary to improve clinical outcomes.[8] The increased prevalence of antibiotic resistance is particularly disconcerting in treating urinary tract infections (UTIs). The presence of metallo-β-lactamase strains of Enterobacteriaceae, which harbor the NDM-1 genes, has been reported to be on the rise in Pakistan in recent metanalysis conducted within the past few years, with both *E. coli* ST405 and *K. pneumoniae* ST11, which produce metallo-β-lactamases, as the dominant resistant strains.[5] Colistin is among the treatment options, but high resistance rates have been reported in many studies.[6,7] Thus, they are unfavorable alternatives for UTIs because of adverse effects and myriad contributing factors. To date, ceftazidime–avibactam and meropenem–vaborbactam are emerging as successful alternatives against carbapenem-resistant strains,[5,6] but ceftazidime-avibactam has only recently become available in Pakistan. Fosfomycin is a broad-spectrum bactericidal with both gram-positive and gram-negative activity, and its oral availability is a particularly important asset in treating UTIs when other agents are ineffective.[7-10] Targeted therapy for UTIs includes active oral antibiotics such as cotrimoxazole and ciprofloxacin, but is used based on sensitivity patterns rather than empiric prescribing.[9,10]

METHODS

This was a retrospective study conducted at Shalimar Hospital, Lahore, where we analyzed urine culture and susceptibility data from the microbiology department after approval from Institute Review Board (IRB) 0769 with reference no SMDC-IRB/AL/2024-110 on dated 6th Nov 2024. 349 urine cultures from 1st January 2024 to 30th June 2024 were considered, excluding repeat samples, duplicate isolates, and mislabeled specimens. Over 6 months, 349 midstream urine samples were collected from male and female patients with the symptoms of UTIs. Sample size was calculated by WHO calculator with prevalence 65.1%, 95% confidence interval and 5% margin of error.[11] One hundred forty-six samples revealed the growth of uropathogens for whom we assessed the susceptibility trends for tier A agents. Uropathogens including *Enterobacterales, Enterococcus, MSSA, coagulase-negative staphylococcus, Group B streptococcus, Acinetobacter baumannii, Pseudomonas spp, and Pseudomonas aeruginosa*, using the CLSI M100, 34th edition breakpoints.[12]

Participants were provided with sterile, wide-necked containers for urine collection. Samples were processed immediately; if delayed, they were refrigerated at 4°C until processing. Midstream urine samples were cultured on Cystine Lactose Electrolyte Deficient (CLED) agar and Blood agar with 0.01 mL calibrated loops. Culture plates were incubated at 37 °C for 24-48 hours, and the isolated microorganisms were identified using conventional identification methods such as API (BioMerieux).

Antimicrobial susceptibility testing was performed by disc diffusion based on CLSI M100, 34th edition.

Information on patient demographics and laboratory results were obtained from the hospital information management system, including susceptibility results for Fosfomycin, nitrofurantoin, cotrimoxazole, ciprofloxacin, tetracycline, meropenem, gentamicin, ceftriaxone, and Amoxicillin-clavulanate. No cost data of clinical measures were obtained.

The clinical and microbiological records were collected and analyzed through the Statistical Package for Social Sciences (SPSS) version 24.0, and the descriptive statistics were expressed as frequencies and percentages.

RESULTS

Over six months, 512 urine samples were submitted to the laboratory for culture. Among them, 146 samples tested positive for uropathogens, including Gram-negative and Gram-positive microorganisms and yeast. Of these positive cases, 69 specimens (47.2%) were from male patients, while 77 specimens (52.8%) were from female patients. (Table 1)

Escherichia coli was the most commonly isolated species, accounting for 65.7% (96/146) of the uropathogens. (Figure 1) Additionally, other microorganisms that are part of the normal intestinal flora were identified as uropathogens in urine culture, including *Enterococcus spp* (12.3%), *Klebsiella pneumoniae* (5.5%), *Candida albicans* (4.8%), and other *Candida* species (2.7%).

The antimicrobial susceptibility against Tier A agents of the frequently isolated gram-negative rods in urine is presented in the Table.2 A low level of resistance has been observed for *E. coli* against meropenem (10%), nitrofurantoin (6%), and Fosfomycin (5%). The ceftriaxone resistance pattern among all gram-negative isolates is quite similar, with striking figures against *E. coli* (82%), *K. pneumoniae* (65%), and *P. mirabilis* (33%). Amoxicillin-clavulanate also had high resistance rates in all microorganisms, including *E. coli* (85%) and *K. pneumoniae* (62%). Piperacillin-tazobactam is the most sensitive antibiotic after meropenem, with the lowest resistance against *P. mirabilis* (0%), *E. coli* (22%), and *K. pneumoniae* (20%). Nitrofurantoin resistance is more in *K. pneumoniae* (38%) as compared to *E. coli* (6%). Fosfomycin is the most sensitive antibiotic against *E. coli*, with the least resistance (5%).

Table 1: Gender-wise distribution of individuals with urinary tract infections

Gender	Positive % (n)	Negative % (n)	Total % (n)
Male	47.2(69)	43.2(158)	44.3(227)
Female	52.8 (77)	56.8 (208)	55.7(285)
Total	28.4 (146)	71.6 (366)	100% (512)

n, number of isolates; %, percentages of isolates.

Table 2: Antibiotic resistance of Gram-negative rods isolated (%)

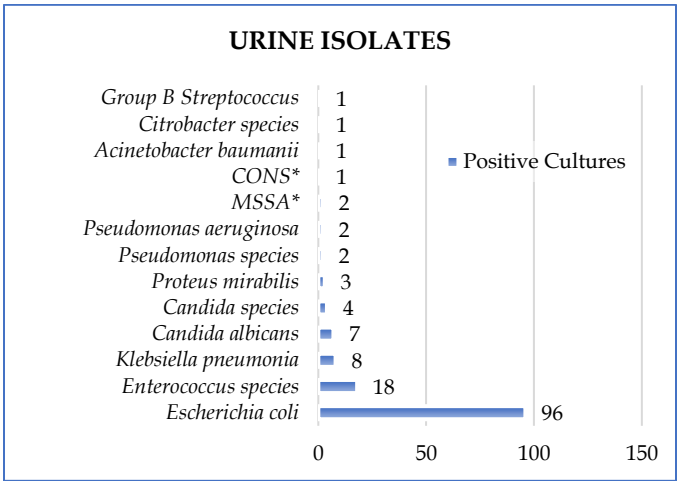
Antibiotic	*Escherichia coli*	*Klebsiella Pneumoniae*	*Proteus mirabilis*	*Pseudomonas aeruginosa*
Ciprofloxacin	76	62	66	50
Nitrofurantoin	6	38	IR	NT
Fosfomycin	5	NT	NT	NT
Ceftriaxone	82	65	33	IR
Meropenem	10	11	0	50
Gentamicin	49	45	33	NT
Cotrimoxazole	63	50	66	IR
Amox-clav	85	62	66	IR
Piper-Tazo	22	20	0	50

Table 3: Microorganiss isolated from patients with UTIs (n=146)

Microorganism	No of isolates	Percentages (%)
Escherichia coli	96	65.7
Enterococcus species	18	12.3
Klebsiella pneumoniae	8	5.5
Candida albicans	7	4.8
Candida species	4	2.7
Proteus mirabilis	3	2.1
Pseudomonas species	2	1.37
Pseudomonas aeruginosa	2	1.37
MSSA*	2	1.37
CoNS*	1	0.68
Acinetobacter baumanii	1	0.68
Citrobacter species	1	0.68
Group B Streptococcus	1	0.68

CoNS – Coagulase Negative Staphylococci MSSA – Methicillin Sensitive Staphylococcus aureus

Figure 1: Frequency (%) of urine isolates



DISCUSSION

Urinary tract infection (UTI) is a primary public health issue worldwide because it is the second most frequent bacterial infection, impacting people of all ages. Between 94 and 96 percent of urinary tract infections result from bacterial infections. *Escherichia coli* is still the most common cause of urinary tract infection (UTI) worldwide.[6] At the same time, the emergence of carbapenem-resistant bacterial pathogens responsible for both healthcare-associated and community-acquired UTIs has posed considerable challenges in clinical management and therapeutic decision-making. This study shows that most uropathogens were isolated from female patients (52.8%), which is consistent with previous studies.[6,13] This imbalance is due to various predisposition factors that increase the chance of developing a UTI in females.[14,15] Females anatomically present shorter urethra, and the location of the urethra near the anus increases the risk of uropathogens such as *E. coli*.[16] Sexual intercourse in females translocates bacteria up the urethra, causing "honeymoon cystitis".[17]

A reported case from Maharashtra, India, in 2022, describes honeymoon cystitis in a young female. It has been hypothesized that the transfer of *Escherichia coli* from the perianal area to the urethra during sexual contact is responsible, and this phenomenon results in honeymoon cystitis. This syndrome can develop after the first sexual contact or resumption of sexual intercourse after prolonged abstinence.[18]

Notably, the overall prevalence of UTI in our study was 28.5%, again showing a slight decline compared to previously reported results in the literature.[6] In our study, *E coli* was the predominant organism causing UTI (65.7%), followed by *Enterococcus spp* (18%) and *Klebsiella pneumoniae* (8%). These findings are similar to those of previous studies done in Pakistan. The only difference is

the prevalence of *Klebsiella pneumoniae* (15%), which is high in our study.[6]

The discovery of penicillin began the antibiotic era, which has played a central role in modern medicine. Although these medicines have been indispensable in saving numerous lives, their over-reliance and abuse, in particular in poorly regulated healthcare regions like Pakistan, have contributed to antibiotic resistance to compromising their effectiveness and public health risk.[17] According to our study, Fosfomycin had the highest sensitivity against *E. coli* (95%), followed by nitrofurantoin and meropenem. Single best sensitivity among meropenem and Tazobactam-Piperacillin was shown by *Klebsiella pneumoniae*, but Fosfomycin was not reported in it as it is not recommended by CLSI. [11] These findings are quite similar to another regional study conducted at Quetta, Pakistan, 2021.[19]

Fosfomycin is a first-line agent for uncomplicated UTIs owing to its broad spectrum, single-dose administration, and low propensity for resistance development. Studies have shown that nitrofurantoin and Fosfomycin were effective against *Escherichia coli*, and both drugs were found to have good tolerance in pregnant women and older patients with renal problems. [20] Recent in vitro data show that nitrofurantoin and Fosfomycin have better activity against *Escherichia coli*. Fosfomycin is included in current clinical guidelines directed at the outpatient treatment of uncomplicated cystitis according to the Infectious Diseases Society of America (IDSA) 2023 and the Sanford Guide to Antimicrobial Therapy, but 1st line agents for treating uncomplicated cystitis are nitrofurantoin and cotrimoxazole, with Fosfomycin only as an alternative option.[21-22]

While Tazobactam-piperacillin is not preferred to meropenem for ESBL-producing isolates, few studies showed no difference in the outcomes from the analytical use of piperacillin-tazobactam in contrast with carbapenems for the treatment of ESBL UTIs, including complex cystitis and pyelonephritis. [23-26]

Amoxicillin-clavulanate is routinely used for uncomplicated and complicated UTIs due to the most susceptible organisms, including non-ESBL *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*. [27] Amoxicillin-clavulanate does not demonstrate a good sensitivity pattern in our study, with *Proteus mirabilis* being the most sensitive.

A Novel recently published in 2024 even showed that patients treated with amoxicillin/clavulanate had a shorter total duration of therapy compared with those receiving standard of care. However, it has some limitations, such as the small sample size and limitations in detecting some other causes of clinical failure. [27]

In oral drugs, Ciprofloxacin and Cotrimoxazole were tested, and more than 50% resistance was shown for all isolates. This sensitivity pattern limits their use as 1st line agents in treating Uncomplicated UTIs caused by Gram-negative rods, such as *E. coli*. These figures are consistent with a local study performed in Pakistan in 2024.[28]

CONCLUSION

This study highlights the daunting situation of the emergence of antimicrobial resistance globally among uropathogens with limited therapeutic options. This alarming situation accentuates the significance of routine antimicrobial susceptibility and trend surveillance for microorganisms causing urinary tract infections. This would be instrumental in the effective empirical treatment of urinary tract infection cases in our setup and prevent injudicious use of antimicrobials while promoting antimicrobial stewardship.

LIMITATIONS

This study has a few limitations. Firstly, it was conducted at a single center, so the findings may not fully apply to other settings. Due to budget limitations, we were unable to perform any molecular analysis. Additionally, we didn't monitor the clinical responses of patients to oral antimicrobials as part of this study. Antimicrobial susceptibility of all isolates was not done in our study because the sample size of the other isolates was very small.

SUGGESTIONS / RECOMMENDATIONS

We recommend further clinical trials with a larger sample size to validate the results of this study. We also recommend the implementation of antibiotic stewardship.

CONFLICT OF INTEREST / DISCLOSURE

Authors report no conflict of interest in this research.

ACKNOWLEDGEMENTS

We are thankful to all staff of lab and all authors for their contribution and efforts.

FUNDING SOURCES

Self-funded.

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