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Original Research Article

Rising Antimicrobial Resistance in Uropathogenic E.coli: Exploring Fosfomycin Role in Current UTI Management

Article History:

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Abstract: ***Introduction:*** Escherichia coli (E.coli) plays a key role in Urinary tract infection globally. There has been an exponential rise in the emergence of multidrug-resistant E.coli, mediated by beta-lactamase enzymes including extended-spectrum beta-lactamases (ESBL), AmpC beta-lactamases, and carbapenemases. Fosfomycin has re-emerged as a potential substitute for treating UTIs triggered by resistant strains. ***Materials and Methods:*** This prospective study, conducted in the Department of Microbiology, Santosh Medical College & Hospital, Ghaziabad, between September 2024 and February 2025, analysed 2,160 non-duplicate midstream urine samples. From these, 243 E. coli isolates were recovered. Antimicrobial susceptibility was determined via the Kirby–Bauer disc diffusion method following CLSI 2024 guidelines. Isolates were further screened and confirmed for ESBL, AmpC, and carbapenemase production using standard phenotypic methods. Fosfomycin susceptibility was initially assessed by disc diffusion, with provisions to detect minimum inhibitory concentration (MIC) via agar dilution for any resistant strains. ***Results:*** Among the 243 E. coli isolates, ESBL, AmpC, and carbapenemase production alone was observed in 16.88%, 2.1%, and 2.1% of isolates, respectively. Simultaneous production of beta-lactamases was detected in 35.8% of isolates, with ESBL and AmpC co-production being the most common. Carbapenemase-producing E. coli constituted 9.9% of isolates. All the isolates demonstrated 100% susceptibility to fosfomycin. High resistance was noted against 3rd and 4th generation cephalosporins, though relatively lower resistance was observed to nitrofurantoin and amikacin. ***Conclusion:*** Fosfomycin demonstrated uniformly high in-vitro effectiveness against multidrug-resistant uropathogenic E. coli.

Keywords: Extended-Spectrum Beta-Lactamases, AmpC Beta-Lactamases, Carbapenemase, Urinary tract infection

INTRODUCTION

Urinary tract infections (UTIs) are very common both

in healthcare and outside settings, and are responsible for around 150 million cases worldwide annually. As a result, the healthcare system faces a huge financial impact. The principal causative agents responsible for UTIs are uropathogenic Escherichia coli (UPEC), causing 80-85% of cases. There is a worldwide rise in the multidrug-resistant (MDR) UPEC strains, mainly due to improper use of antimicrobials, especially beta-lactam antibiotics, in the empirical treatment of UTIs.1

Beta-lactam antibiotics become resistant in treating bacterial infection by various mechanisms, for example, production of beta-lactamase enzymes like Extended-spectrum beta-lactamase (ESBL), AmpC beta-lactamases, and carbapenemases.2

ESBLs were first isolated from Western Europe in 1980. ESBLs, which are acquired from the existing broad-spectrum beta-lactamases, have an extended substrate profile allowing them to hydrolyse all cephalosporins, penicillins, and aztreonam. As per the available literature, more than 300 ESBLs have been identified based on their physical properties. Extended-spectrum beta-lactamase (ESBL) production, being plasmid-mediated enzymes, can easily be transmitted from one organism to another.3 AmpC beta-lactamases are clinically substantial enzymes that hydrolyse cephalosporins, cephamycins, aminopenicillins, and monobactams. Notably, they are poorly inhibited by clavulanic acid and can arise through both chromosomal and plasmid-mediated mechanisms.

Furthermore, the heavy reliance on carbapenems for treating severe infections has led to the rise of carbapenemase-producing Gram-negative bacilli. Common variants of these enzymes include Klebsiella pneumoniae carbapenemase (KPC), Verona integron metallo-beta-lactamases (VIM), OXA-48, NDM-1, and IMP types, all of which pose significant challenges to antimicrobial therapy.4

Fosfomycin is a broad-spectrum antibiotic mainly indicated for uropathogens like E.coli. It is a derivative of phosphonic acid. It inhibits the initial steps of peptidoglycan synthesis by inactivating cytosolic N-acetyl glucosamine enolpyruvyl transferase (MurA). Resistance to fosfomycin is bestowed due to defects in the transmembrane transporters, mutations in the MurA active site that reduce fosfomycin binding affinity and production of FosA, a fosfomycin-inactivating enzyme that is a Mn2+- and K+- dependent glutathione S-transferase.5

Fosfomycin has also shown substantial activity in suppressing multidrug-resistant (MDR)microorganisms producing biofilms.5

Hence, this study was conducted to assess the Fosfomycin resistance amongst ESBL, AmpC and carbapenemase-producing uropathogens.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Microbiology, Santosh Medical College & Hospital, Santosh Deemed to be University, Ghaziabad, from September 2024 to April 2025. A total of 2160 non-duplicate, clean catch Midstream urine samples from symptomatic patients from both the inpatient department (IPD) and outpatient department (OPD) settings were enrolled in the study.

Samples were collected and relocated to the laboratory according to recommended guidelines to avert contamination.[6]

Isolation and identification: A direct wet mount was prepared to detect the presence of inflammatory cells and microbial flora. The urine specimens were plated onto cystine-lactose-electrolyte-deficient (CLED) agar.. Only one type of colonies $>10^5$ per ml urine was considered significant. Statistically Significant strains were determined according to the standard criteria.[6]

Antimicrobial susceptibility testing (AST): All isolates of E. coli with significant growth were included in the study. Susceptibility testing followed CLSI 2024[7] recommended, using *E. coli* ATCC 25922 as the quality control strain.

Screening and Confirmation of ESBL production: All E. coli isolates were screened for ESBL by disc diffusion method with Ceftazidime (30µg), Cefotaxime (30µg), Ceftriaxone (30µg) and Aztreonam (30µg). These isolates were confirmed using a phenotypic confirmatory double disc (Ceftazidime 30µg and Ceftazidime-clavulanate 30µg +10µg) test.[7] Control strains *E. coli* ATCC 25922 and K. *pneumoniae* ATCC 700603 were included in the study. (Figure-1).

Screening and Confirmatory test for AmpC production: All the isolates with an inhibition zone diameter of ≤18mm for cefoxitin were labelled as AmpC positive and were subjected to a confirmatory test (Boronic acid and Cloxacillin Double disk test).[8] (Figure-2)

Screening and Confirmatory test for Carbapenemase production: All the *E. coli* isolates were screened for carbapenemase production by susceptibility testing (Kirby Bauer disk diffusion method) to imipenem (10µg) and meropenem (10µg) antibiotic discs (Himedia, Mumbai). All isolates showing an inhibition zone of ≤19 mm were selected as screen positive for carbapenemase production, and a confirmatory test (mCIM) was performed.[7] The quality control strain was *E. coli* ATCC 25922. (Figure-3)

Detection of fosfomycin resistance by Kirby Bauer disk diffusion method: The inhibition zone≥ 16mm, 13-15mm, and ≤ 12mm were interpreted as sensitive, intermediate and resistant in accordance to CLSI guidelines 2024.[7]

Figure 1: Phenotypic confirmatory test for detection of ESBL production in *E. Coli*

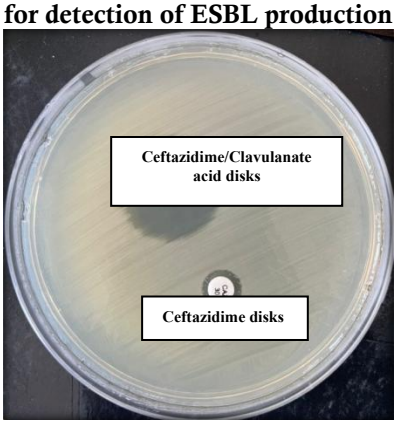


Figure 2: Phenotypic confirmation test for detection of AmpC production in *E. Coli*

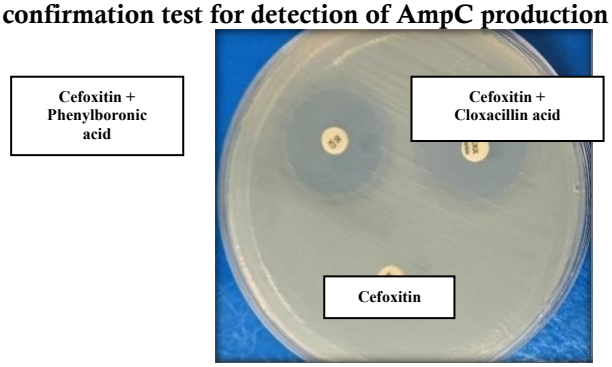
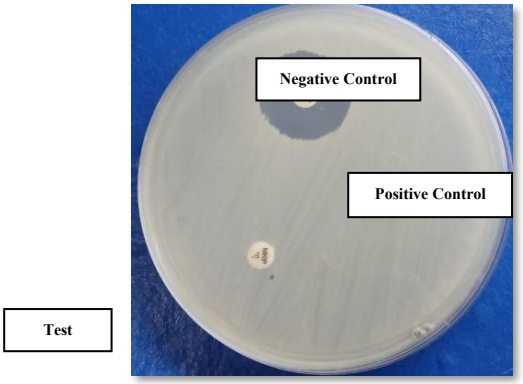


Figure 3: Phenotypic confirmation test (mCIM) for detection of Carbapenemase production in *E. coli*



RESULTS

Overall, 243 *E.coli* isolates were obtained from 2160 urine samples during the study period. Gender & age - wise distribution of the patient is shown in **Table-1**.

Out of 243 *E.coli* isolates, 60 (25%) were from the out-patient department, 135 (55%) from the In-patient department and 48 (20%) from the Intensive care unit (ICU), respectively.

Table-2 Illustrates the production of beta - lactamases by *E.coli* strains isolated from the urine sample. All the 243 ESBL ,AmpC and carbapenemase-positive *E.coli* isolates were sensitive to fosfomycin.

Antimicrobial resistance of isolated *E.coli* shows that the maximum isolates were resistant to cefotaxime 78%, followed by Ceftriaxone 76%, Ceftazidime 51.85%, Cefixime and Cefepime 51.85% each, Ciprofloxacin 35.8%, Piperacillin-tazobactam 27.16%, Cotrimoxazole 27.16%, Gentamicin 19%, Nitrofurantoin 10%, Amikacin 9.5%, and the least resistance was observed for Carbapenem 9%. All *E.coli* isolates were sensitive to fosfomycin. (Figure-4)

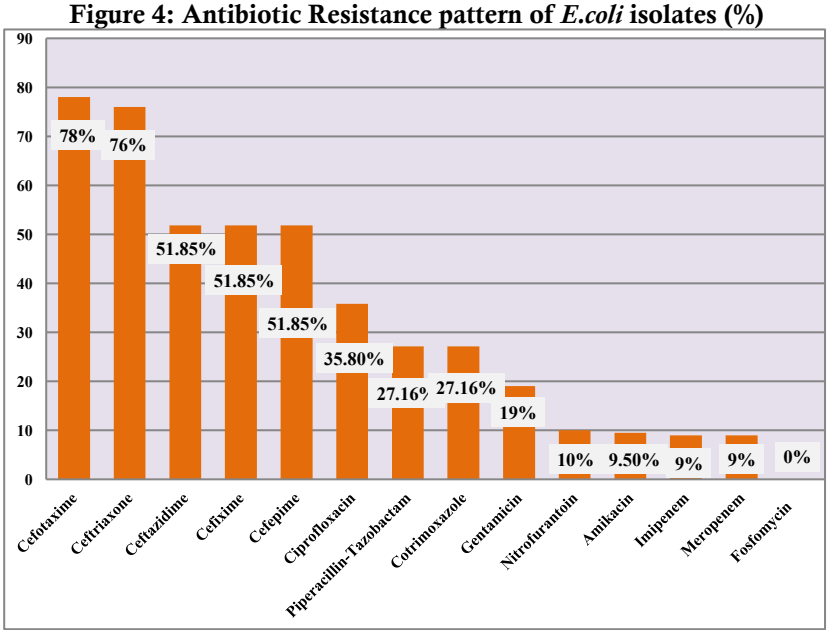
Table1 :Distribution of patients according to gender, age - group and source of study cases*E.coli* strains causing UTI (N=243)

Variable	Number (%)
Gender	
Male	138 (56.8 %)
Female	105 (43.2 %)
Age (Years)	
18-30	103 (42.5%)
31-40	52 (21.4%)
41-50	32 (13.1%)
51-60	21 (8.6 %)
Above 60	35 (14.4%)
Source of sample	
Out - patient department (OPD)	60 (25%)
In-patient department (IPD)	135 (55 %)
Intensive care unit (ICUs)	48 (20%)

Table 2: Beta - lactamases production by *E.coli* strains causing UTI and their resistance to fosfomycin (N=243)

Beta Lactamase	Total number of Isolates	Percentage (%)	Resistance to fosfomycin
ESBL	41	16.88	0
AmpC	5	2.1	0
MBL	5	2.1	0
ESBL+AmpC	65	26.75	0
ESBL+MBL	3	1.23	0
AmpC+MBL	0	0	0
ESBL+AmpC+MBL	19	7.8	0

Figure 4: Antibiotic Resistance pattern of *E.coli* isolates (%)



DISCUSSION

UTI is one of the most common infections seen in all age groups and both genders. Commonly isolated uropathogens are increasingly becoming multidrug-resistant and rendering the commonly available oral antibiotics ineffective.

In the present study, the prevalence of E. coli causing UTI was higher in males (56.8%) than in females (43.2%). This is similar to a study done by Lohariwal et al.,9 where 53.40% of males and 46.59% of females were affected by UTI. Male preponderance observed in the present study may be attributed to the rural and conservative nature of the study population. In such settings, men tend to access healthcare facilities more readily, whereas women often ignore urinary symptoms or exhibit inhibition in seeking medical care due to socio-cultural barriers.

In the current study, there was a higher prevalence of UTI in the 18 to 30 years age group, which is aligned with observations made by Garg N et.al.10 and Jain R et.al.11 The increased occurrence of urinary tract infections in the 18–30 year age group may be related to greater sexual activity during this period. Additionally, pregnancy-associated physiological changes could further contribute to the higher incidence observed among females in this age group. Globally, there is a rampant increase in the beta-lactamase-producing uropathogens, both in the society and hospital. These are often associated with serious UTI.

In this study, the prevalence of E.coli producing ESBL, AmpC, and MBL, alone, was found to be 16.88%, 2.1%, and 2.1%, respectively. Prevalence of co-producers of ESBL &other beta lactamases was 35.8%, which is more than the number (16.88%) of isolates producing ESBL alone. This could be due to the coexistence of several resistance genes in the plasmids, which are transferred horizontally among the various isolates. This further aggravates the problem of antimicrobial resistance worldwide. In another study done by Chaudhary U et.al,12 co-production of beta lactamses was found to be27%, which is lower when compared to our study.

In our study, altogether ESBL production (both alone and coproduction along with other beta-lactamases) was observed in 52.6% of E.coli isolates. Numerous studies have shown similar result11 or even higher rates of isolation of ESBLs 65.30%13 and 74.15%14. In the present study, AmpC production was exhibited by 38% of E.coli isolates, which is consistent with other studies such as Bora A et al.,15 from Assam (28.96%) and Shreshtha UT et. al.16 (46.3%). However, there is a minimal rate of detection of the AmpC producers, in other studies. 17, 18

The prevalence of coproduction of AmpC among ESBLs was 27.58% in our study, which is slightly higher when compared to the findings reported by Gupta V et al.,19 (8.0%), Mwinga MM et. al.,20 (10.77%) and Shreshtha UT et al., (19.4%)16.

The proportion of carbapenemase - producing E.coli detected in the present study was 9.9%. Other studies also exhibited variable prevalence; Shreshtha UT et al.,16 (11.2%), Mwinga MM et. al.,20(18.4%). Coproduction in the recent study was 7.9%, which is less than in other studies. 21,22 Co-production of ESBL and MBL was seen in 1.24% of isolates.

The leading outcome in our study is 100% susceptibility of uropathogenic E.coliisolates to fosfomycin. Similar high susceptibility to fosfomycin was also observed by several recent studies.18,23,24 However, considerable studies have shown resistance to fosfomycin among E.coli causing UTI.11,13,14 Though the resistance is quite minimal at present. This could be due to the long duration of their study. Fosfomycin is sparingly used, hence there is less selective pressure resulting in slower resistance development. Fosfomycin maintains urinary concentration above the minimum inhibitory concentration for 24-48 hours following a single 3-gram oral dose. We conducted our study for four months. So, further studies are required to observe the fosfomycin resistance in our setup.

In addition to fosfomycin, very good susceptibility was observed towards nitrofurantoin and amikacin in our study. Another study done by Azad MS et.al25, showed (11%) nitrofurantoin and (16%) amikacin resistance, which is similar to our study. The present study has revealed significant resistance towards cefotaxime, ceftriaxone, ceftazidime, cefixime and cefepime. Numerous other studies showed similar resistance to these drugs.(15,20) Both these antibiotics were useful in multidrug - resistance and ESBL-producing isolates in the present study.

Several reasons may contribute to a high burden of antimicrobial resistance in one region. Improper and irrational prescription of antimicrobials, prescription of broad-spectrum antibiotics without any sensitivity testing, availability over the counter (OTC), self-medication, poor patient compliance with the treatment schedule, low access to health care services by the community, lack of implementation of hospital antibiotic policy and inadequate infection control measures have been identified as major factors leading to a high level of resistance in an area. This fast horizontal co-transfer of resistance genes supported by plasmids, among different bacteria, also contributes to the acquisition and spread of beta-lactamase-producing strains in the environment, particularly within health care units.

Limitation

This study was conducted for a short duration and at a single centre. This study should be extended for a longer duration, and a multicenter study gives a much better picture of fosfomycin resistance among uropathogens.

CONCLUSION

Unjustified and indiscriminate use of antimicrobials plays a significant role in the development of antimicrobial resistance, which has become a foremost challenge in the treatment of urinary tract infections. The increasing resistance among uropathogens, particularly multidrug-resistant Escherichia coli, has abridged the effectiveness of commonly used antibiotics. In such situations, fosfomycin serves as a useful alternative for the treatment of urinary infections caused by MDR E. coli isolated from urine. Judicious use of this drug, supported by culture and sensitivity results, is essential to ensure its continued effectiveness and to limit further emergence of resistance.

REFERENCES

1. Singla P, Sangwan J, Singh P, Mane P, Yadav K, Singh NK. Increasing antibiotic resistance in uropathogenic Escherichia coli: Is Fosfomycin a promising alternative?. Surgery.;27:16.
2. Chanu TR, Shah PK, Soni S, Ghosh AN. Phenotypic detection of extended spectrum, AmpC, Metallo beta-lactamases and their coexistence in clinical isolates of commonly isolated gram negativebacteria in GKGH hospital, Bhuj. IP International Journal of Medical Microbiology and Tropical Diseases. 2023 Jan 23;5(1):52-6.
3. Nasir KM, Preeti S, Vikili C, Singh NP. Prevalence of ESBL and AmpC βlactamase in gram negative bacilli in various clinical samples at tertiary care hospital. Int Res J Medical Sci. 2015 Aug;3(8):1-6.
4. Ibadin EE, Omoregie R, Anogie NA, Igbarumah IO, Ogefere HO. Prevalence of extended spectrum β-Lactamase, AmpC β-Lactamase and Metallo-β-Lactamase among gram negative bacilli recovered from clinical specimens in Benin City, Nigeria. International Journal of Enteric Pathogens. 2017 Jul 19;5(3):85-91.
5. Zdzieblo M, Biernasiuk A, Helon P, Malm A. Fosfomycin activity against strains isolated from urine specimens. Current Issues in Pharmacy and Medical Sciences. 2023;36(4):217-20.
6. Collee JG, Marr W. Culture of bacteria. In: Collee JG, Fraser AG, Marmion BP, Simmons A, eds. Mackie and McCartney Practical Medical Microbiology, 14th ed. New York: Churchill Livingstone; 2006:113–129.
7. Clinical and Laboratory Standards Institute (CLSI).Performance Standards for Antimicrobial Susceptibility Testing;Twenty nine informational supplement 2024;39:M100-S29.
8. Gupta G, Tak V, Mathur P. Detection of AmpC β lactamases in gram-negative bacteria. Journal of laboratory physicians. 2014 Jan;6(01):001-6.
9. Lohariwal Y, Das NK, Mirza S, Gandham N, Patil R, Mukhida S, Shah H, Khan S. Fosfomycin susceptibility among Escherichia coli causing urinary tract infection in a tertiary care centre in Western Maharashtra. IMC J Med Sci. 2023;17:1-6.
10. Garg N, Bachhiwal R, Sharma R. Fosfomycin susceptibility in multidrug-resistant uropathogenicEscherichia coli isolates at a tertiary care hospital in Jaipur, Rajasthan, India. Indian J Microbiol. 2024;16(6):021-026.
11. Jain R, Pal N, Hooja S. Prevalence of β-lactamase production and multi-drug resistance among uropathogenic Escherichia coli isolates at a tertiary care hospital of North-western India. Asian Journal of Medical Sciences. 2021 Jul 1;12(7):27-32.
12. Chaudhary U, Agarwal S, Raghuraman K. Identification of extended spectrum beta lactamases, AmpC and carbapenemase production among isolates of Escherichia coli in North Indian tertiary care centre. Avicenna journal of medicine. 2018 Apr;8(02):46-50.
13. Dalai S, Modak M, Lahiri K. Fosfomycin susceptibility among uropathogenic E. coli and K.pneumoniae. IJSR 2019;8:282 4.
14. Sreenivasan S, Kali A, Pravin Charles MV, Kunigal S. Evaluation of in vitro susceptibility of fosfomycin among Enterobacteriaceae isolates from urine cultures: A study from Punducherry. J Lab Physicians 2019;11:249 52.
15. Bora A, Ahmed GU and Hazarika NK .Phenotypic detection of extended spectrum β-lactamase and AmpC β-lactamase in urinary isolates of Escherichia coli at a tertiary care referral hospital in Northeast India. JCMS Nepal.2012; 8:1-8. https://doi.org/10.3126/jcmsn.v8i3.8682.
16. Shrestha UT, Shrestha S, Adhikari N, Rijal KR, Shrestha B, Adhikari B, et al. Plasmid profiling and occurrence of β-lactamase enzymes in multidrug-resistant uropathogenic Escherichia coli in Kathmandu, Nepal. Infect Drug Resist. 2020; 13:1905-1917. https://doi.org/10.2147/IDR.S250591.
17. Tan CW and Chlebicki MB. Urinary tract infections in adults. Singapore Med J.2016; 57:485-490. https://doi.org/10.11622/smedj.2016153.
18. Bakshi R, Sehgal VK, Kansal P and Kaur S. Detection of Extended-Spectrum Beta Lactamases and AmpC Beta Lactamases Producing Uropathogenic Escherichia coli in a

TertiaryCareHospital.IJMDS.2019;8(2):1783-1792. https://doi.org/10.18311/ijmds/2019/23503.

19. Gupta V, Rani H, Singla N, Kaistha N and Chander J. Determination of extended-spectrum β-lactamases and AmpC production in uropathogenic isolates of Escherichia coli and susceptibility to fosfomycin.JLP.2013;5:90-93. https://doi.org/10.4103/0974-2727.119849.
20. Mwinga MM, Mahale RP and MN Sumana. Phenotypic detection of AmpC β lactamase and metallo β lactamase production among uropathogenic E.coli. IJSR.2018; 7:68-71. https://www.doi.org/10.36106/ijsr.
21. Rawat V, Singhai M, Verma PK. Detection of different β lactamases and their co existence by using various discs combination methods in clinical isolates of Enterobacteriaceae and Pseudomonas spp. J Lab Physicians 2013;5:21 5.
22. Oberoi L, Singh N, Sharma P, Aggarwal A. ESBL, MBL and AmpC β lactamases producing superbugs – Havoc in the Intensive care Units of Punjab India. J Clin Diagn Res 2013;7:70 3.
23. Sardar A, Basireddy SR, Navaz A, Singh M, Kabra V. Comparative evaluation of fosfomycin activity with other antimicrobial agents against E. coli isolates from urinary tract infections. Journal of clinical and diagnostic research: JCDR. 2017 Feb 1;11(2):DC26.
24. Shakthi R, Venkatesha D. Fosfomycin susceptibility among extended-spectrum beta-lactamase producing and carbapenem-resistant uropathogens. Int J Acad Med Pharm. 2023;5(2):1185-1188. doi: 10.47009/jamp.2023.5.2.251.
25. Azad MS, Kumari S, Jha K, Sharma RN. Resurgence of nitrofurantoin and fosfomycin as effective oral empirical treatment options for multidrug resistant uropathogens. Int J Acad Med Pharm. 2024;6(4):616-21.

