ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 11, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

FOSFOMYCIN SUSCEPTIBILITY IN MULTIDRUG-RESISTANT UROPATHOGENS: A RETROSPECTIVE STUDY IN THE ERA OF ANTIMICROBIAL RESISTANCE

JASLEEN KAUR, PRIYA BHAT, UPASANA BHUMBLA*

Department of Microbiology, Adesh Institute of Medical Sciences and Research, Bathinda, Punjab, India.
***Corresponding author: Upasana Bhumbla; Email: ucupasana124@gmail.com**

Received: 19 June 2024, Revised and Accepted: 17 September 2024

ABSTRACT

Objective: Urinary tract infection (UTI) is one of the most prevalent clinical entities affecting people worldwide. The accelerating rate of Antimicrobial resistance due to the unimpeded and rampant use of antimicrobials with over-the-counter availability of drugs has limited the therapeutic options for the treatment of UTIs. Fosfomycin, an old broad-spectrum antimicrobial with good pharmacokinetics has regained importance for the treatment of multidrug-resistant (MDR) isolates. The purpose of this study was to determine the *in vitro* Fosfomycin susceptibility of common uropathogens and to study the resistance pattern of these organisms against commonly prescribed antimicrobial agents.

Methods: A retrospective cross-sectional study was conducted in the Bacteriology section of the Microbiology laboratory at Adesh Institute of Medical Sciences and Research, Bathinda, Punjab for duration of 6 months from December 2022 to May 2023 from urine samples received from all clinically suspected cases of UTI. Samples were processed immediately as per standard microbiological techniques, followed by culture by a semi-quantitative method. Kass criteria was followed for interpretation of significant bacteriuria according to which significant growth was considered if the colony count was more than 10^5 colony forming units (CFU)/mL. Culture positives were analyzed by Gram staining and on the basis of colony characteristics, Gram staining, final identification, and Antimicrobial Susceptibility were done through Vitek 2 compact system.

Results: A total of 2292 urine samples received in the Microbiology laboratory were processed and cultured during the study period, which yielded 509 significant bacterial isolates i.e.509/2292 (22.2%) culture positivity. Among 509 culture-positive samples, *Escherichia coli* 235/509 (46.1%) was the most common uropathogens isolated followed by *Klebsiella pneumoniae* 107/509 (21.1%), *Enterococcus* species 40/509 (7.8%). Fosfomycin depicted good *in vitro* susceptibility of a minimum of 94% in both Gram-negative and Gram-positive uropathogens as compared to Nitrofurantoin, which showed sensitivity of 74% and 85%, respectively. Maximum resistance was observed toward Cephalosporins i.e., Ceftriaxone in *E. coli (*60%) and *K. pneumoniae* (64%), respectively, followed by 50% in *Acinetobacter baumannii*. Maximum resistance to Ciprofloxacin (62%) was seen in case of *A. baumannii*. 172/405(42.4%) isolates of Enterobacteriaceae family were extended-spectrum β-lactamase (ESBL) producers with an average Fosfomycin susceptibility of 95.9%. Among the total isolated uropathogens, 135/509 (26.5%) were MDR, out of which 116/135 (85.9%) depicted Fosfomycin susceptibility. Metallo-beta-lactamase (MBL) production was seen in 14.3% of the isolated Gram-negative uropathogens. 63/73(86.3%) of the MBL producers were found susceptible to Fosfomycin.

Conclusion: Fosfomycin has emerged as an effective alternative for the treatment of common uropathogens including the MDRs, ESBL producers, and the MBLs in the era of increasing antimicrobial resistance. It has the potential to act as a promising oral agent for the treatment of UTI in both community and healthcare setups.

Keywords: Fosfomycin, Uropathogens, Multidrug-resistance, Extended spectrum β lactamase's, Metallo-betalactamase's.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i11.51811. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common ailments associated with significant morbidity and mortality in both Community and healthcare setups [1]. Gram-negative organisms constitute a major burden of the causative agents which are known to harbor multiple drug-resistance either inherited or transmissible against the most routinely used antimicrobial agents. Overuse and misuse of antimicrobials have limited the therapeutic options for the treatment of UTI, which has led to an increase in the prevalence of multidrug-resistant (MDRs) Uropathogens. MDRs are the organisms resistant to any three different classes of antibiotics [2]. Rampant and uncontrolled use of antibiotics has drastically altered the resistance pattern of uropathogens thus leading to treatment failure. Acquired antibiotic resistance can occur because of varied mechanisms, such as (a) the presence of active efflux pumps; (b) altering cell membrane permeability and bypassing of metabolic pathway; (c) alteration of the drug target; and (d) enzymatic inactivation and modification. The production of β-lactamases is the most important mechanism contributing to drug resistance [3]. Extended-spectrum β-lactamases (ESBLs) are the plasmid-mediated enzymes that have the capacity to hydrolyze many β-lactams antibiotics, including third-generation cephalosporins and monobactams [4] whereas Metallo-beta-lactamases (MBLs) are a diverse set of enzymes that catalyzes the hydrolysis of a broad range of β-lactam drugs, including carbapenems (Imipenem, Meropenem) [5]. In the scenario of emerging MDR, the treatment options with oral drugs usually prescribed are becoming limited with the role of injectables in place thus increasing the inpatient hospital stay with increased financial burden even in uncomplicated UTI. Meanwhile, Fosfomycin an old antibiotic has regained its value for the treatment of UTI in MDR uropathogens due to its oral regimen maintaining higher urinary concentration, broad-spectrum coverage against both Gram-positive and Gram-negative bacteria including MDR strains, and minimal cross-resistance with other antibiotics. Hence, Fosfomycin can serve as a wonder drug and a greater therapeutic option in case of uropathogens. Fosfomycin, a phosphonic acid derivative discovered in Spain in 1969, produced by *Streptomyces* spp., acts by inhibition of cell wall synthesis by causing inhibition of phosphoenol pyruvate. It has an oral bioavailability of 40% and the majority of the absorbed drug is excreted unchanged in urine. With such properties, single-time oral therapy with Fosfomycin

has been recommended to treat cases of UTI [2]. It has the potential for the emergence of resistance during therapy, causing the selection of resistant mutants [6]. Keeping in mind the increasing resistance of uropathogens, the present study was undertaken to evaluate the *in vitro* antimicrobial activity of Fosfomycin of commonly isolated uropathogens in comparison to other antibiotics and determining the resistance pattern of these organisms against commonly prescribed antimicrobial agents which can serve as an additional aid for healthcare providers in the treatment of the MDR superbugs.

METHODS

A retrospective observational study was conducted in the Bacteriology section of the Microbiology laboratory at Adesh Institute of Medical Sciences and Research, Bathinda, Punjab. The study period was 6 months for which data were collected (December 2022–May 2023) and analyzed. Institutional Research Committee, Ethics Committee for Biomedical and Health Research, Adesh University permissions were taken before starting the study. Urine samples received in the laboratory with clinical suspicion of UTI whether midstream clean catch urine sample, surgically collected urine samples, and urine received from the catheter with proper surgical asepsis with needle and syringe were included in the study. All the non-duplicate urine samples received in the laboratory for urine culture and sensitivity were processed. Demographic details and clinical information were also collected.

Inclusion criteria

All the non-duplicate bacterial isolates with significant bacteriuria were included in the study.

Exclusion criteria

Improper labeling of the urine samples with incomplete demographic details and clinical data

- Urine samples received from children <12 years.
- Urine samples with fungal isolates
- Repeat samples received for processing.

Study procedure

The samples were received in universal sterile containers appropriately labeled and analyzed within 2 h after collection. Routine microscopic examination of urine samples was done to look for pus cells, red blood cells, casts, and epithelial cells. Urine culture was done by semi-quantitative method in which a loopful 0.001 mL of well-mixed uncentrifuged urine was inoculated on blood agar and Cysteine Lactose Electrolyte Deficient medium agar and incubated for 24–48 h at 37°C aerobically to check for the bacterial growth. The plates were then examined macroscopically for bacterial growth. Kass criteria was followed for interpretation of significant bacteriuria according to which significant growth was considered if number of colony count was more than 10^5 CFU/mL [7].

Culture positives were analyzed by Gram stain and on the basis of colony characteristics, Gram staining, biochemical tests, and final identification were done using the Vitek 2 compact system. Out of the 2292 total urine samples received, 509 samples showed culture positivity. Isolates identified as MDR were further analyzed for their susceptibility to Fosfomycin. For Gram-positive organisms GP card 628 was used and for Gram-negative GN cards 405 and 406 were used. Fosfomycin susceptibility in Gram-positive bacteria and Nitrofurantoin susceptibility in Gram-negative bacteria was done on Mueller Hinton Agar by Kirby Bauer disc diffusion method and zone diameter was interpreted according to the latest CLSI guidelines M100 published in 2022 [8]. In addition to Vitek-2, the potential ESBL producers showing resistance to third-generation Cephalosporins were also manually subjected to phenotypic confirmatory tests, a double-disk synergy test, and a combined disk assay method. For MBL production, all Gram-negative isolates showing resistance to Imipenem and Meropenem antibiotic disks through Vitek-2 were subjected to phenotypic confirmatory tests, an Imipenem-ethylene diamine tetraacetic acid combined disk test, and an Imipenem-etheylenediamine tetraacetic acid double-disk synergy test [4]. Collected data were all compiled in the MS Excel sheet and applicable statically analysis was done. Data were analyzed and the effectiveness of Fosfomycin over other drugs was calculated in frequencies and percentages.

RESULTS

A total of 2292 urine samples were received after fulfilling the inclusion criteria, out of which 509 (22.2%) samples yielded significant growth on culture. 276 (54.3%) were females and 233 (45.7%) were males as shown in (Fig. 1). Mean age of the patient was 38 years, representing the sexually active females. Most of the culture-positive urine samples were from different inpatient department's (47.1%), maximum from Obstetrics and Gynecology, Medicine and Pediatric ward followed by outpatient department (OPD) (39.2%) maximum from Urology and Medicine OPDs, and 7.3% were from Emergency and 6.4% were from intensive care units (ICU's) (Table 1).

Among the culture-positive samples, the most common uropathogens in the present study were members of Enterobacterales—*E. coli* (46.1%), followed by *K. pneumoniae (*21.1%) as shown in Fig. 2.

Among the Gram-negative isolates, lower rates of resistance were observed for Imipenem (14%), Tigecycline (13%), and Colistin (7%). Fosfomycin depicted a good *in vitro* activity of a minimum of 93% in Enterobacterales. Relatively Nitrofurantoin showed a susceptibility of 72% in Enterobacterales. Third-generation Cephalosporins i.e., Ceftriaxone in *E. coli* and *Klebsiella pneumoniae* showed maximum resistance of 60% and 64%, respectively, followed by 50% in *Acinetobacter baumannii*. 55% and 58% of isolates of *E. coli* and *K. pneumoniae* were resistant to Ciprofloxacin. Maximum resistance to Ciprofloxacin (62%) was seen in case of *A. baumannii* as shown in (Fig. 3).

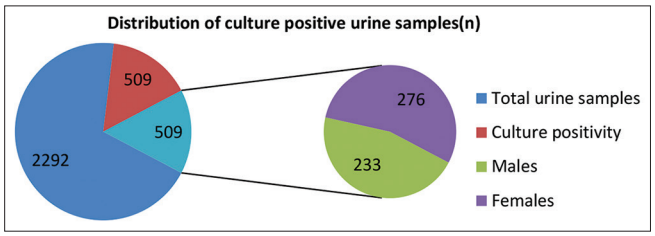

Fig. 1: Pie chart depicting culture-positive urine samples

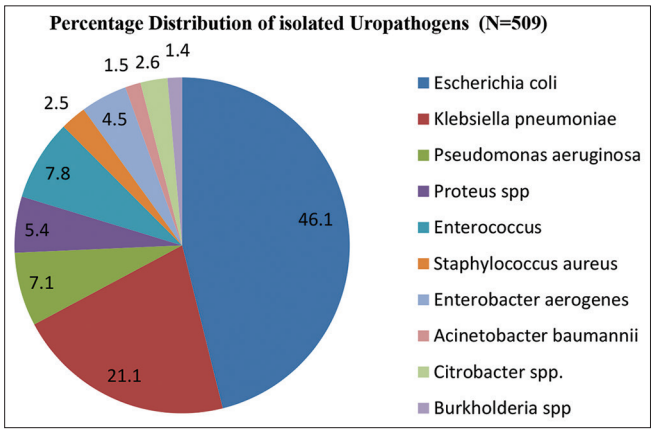

Fig. 2: Distribution (percentage) of isolated uropathogens

Table 1: Department wise distribution of uropathogens

Department	Number of isolates	Percentage
Outpatient Department	200	39.2
Inpatient Department	240	47.1
Emergency	37	7.3
Intensive care unit	32	6.4

Staphylococcus aureus showed maximum resistance toward Benzyl Penicillin (60%) while Linezolid, Vancomycin, and Teicoplanin showed excellent sensitivity of 96%, 96%, and 97%, respectively.

Fosfomycin was effective *in vitro* against 94% and 100% of *S. aureus* and *Enterococcus* spp., respectively, as shown in (Fig. 4).

Maximum ESBL production was seen in *K. pneumoniae* (58.8%) and showed susceptibility for Fosfomycin for 90.9% as depicted in (Fig. 5).

Among all the isolated uropathogens, 26.5% were multidrug-resistance out of which 85.9% depicted Fosfomycin susceptibility. Figs. 6 and 7 depict the distribution (%) of MDR and MBL producing isolates and Fosfomycin susceptibility. MBL production was seen in 14.3% of the isolated Gram-negative uropathogens. 86.3% of MBL producers were found susceptible to Fosfomycin.

DISCUSSION

UTI is one of the primary ailments encountered in both community and healthcare setups. The emergence of resistance to regularly used antibiotics has left limited therapeutic options for UTIs. Hence, there is an increasing need to develop and introduce new antimicrobials for this purpose. With the scarcity of availability of antimicrobials, the old and forgotten antibiotics have retrieved their importance for the treatment of UTIs. Hence, the present study was undertaken to look for Fosfomycin susceptibility among uropathogens. A total of 2292 urine samples were studied for a period of 6 months, (509) 22.2% of which depicted culture positivity. Similar results were shown by studies done by Sharmin *et al.* [9] reported the incidence of UTI as 17.3%. A lower rate of UTI was observed in an Indian study conducted by Singh *et al.* that

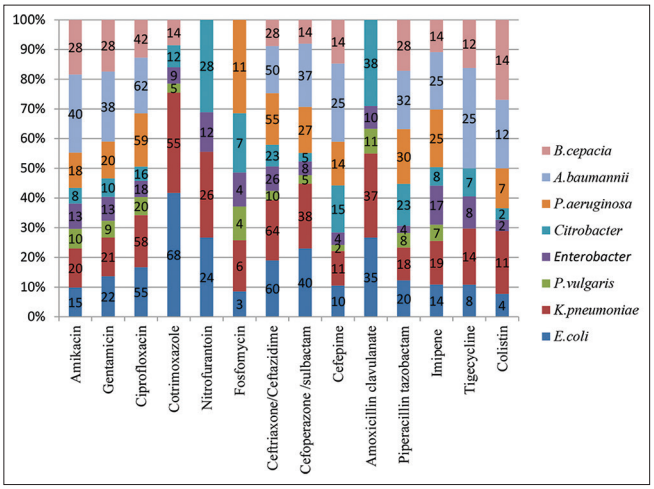

Fig. 3: Antimicrobial resistance (%) of the isolated Gram-negative uropathogens

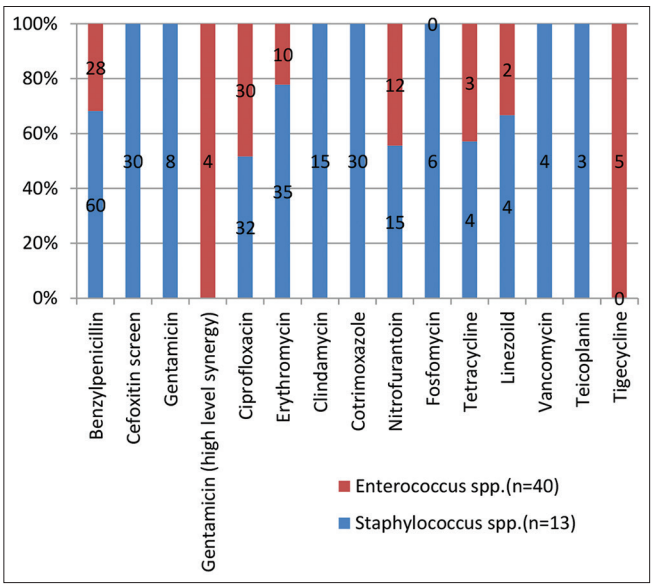

Fig. 4: Antimicrobial resistance (%) of isolated Gram-positive uropathogens

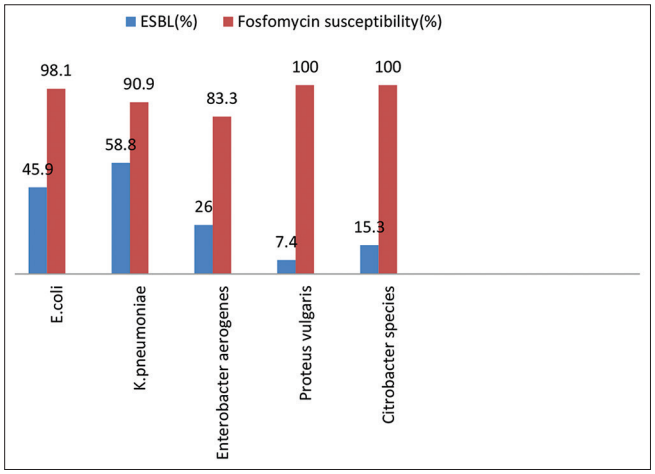

Fig. 5: Fosfomycin susceptibility among extended-spectrum β-lactamases producing isolates of Enterobacteriaceae

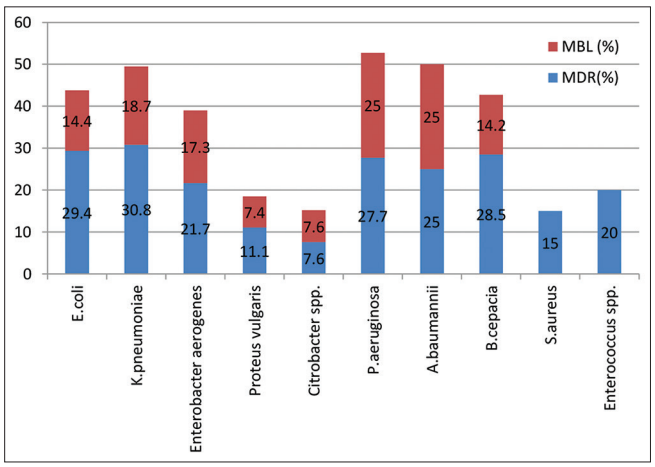

Fig. 6: Distribution (%) of multidrug-resistant and metallobeta-lactamase producing isolates

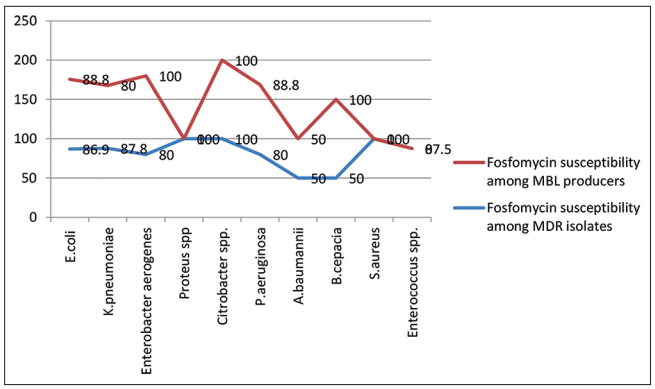

Fig. 7: Fosfomycin susceptibility among multidrug-resistant and metallo-betalactamase producers

depicted the culture positivity of 4.2% [10]. Females (54.3%) showed a higher preponderance than males (45.7%) which was consistent with the data shown by various studies [9,11]. This could be attributed to the shorter urethra and the close proximity of the urethral meatus to the anus in females leading to increased chances of UTI in females. Maximum culture positivity was seen from the samples received from the Obstetrics and Gynecology patients as maximum urine samples were received from there followed by urology OPD. 6.4% of urine samples were from ICU mostly from catheterized patients (Table 1).

Among 509 culture-positive samples, the most common uropathogens isolated was *E. coli 2*35/509 (46.1%) followed by *K. pneumoniae*107/509(21.1%), *Enterococcus species* 40/509 (7.8%) (Fig. 2). Similar results were seen in a study done by Sharmin *et al*. [9] where members of the Enterobacterales- *E. coli (*65.84%), followed by *K. pneumoniae* (16.49%) were the most common uropathogens isolated. Another study conducted by Sharlee and Sumangala [12] found that out of 103 Gram-negative bacilli, the majority were *E. coli* with 29.1% followed by *K. pneumoniae at* 25.3%, *Pseudomonas aeruginosa* 3%, *Acinetobacter* 3%, Enterobacterales 1.9% and *Citrobacter* species 1.2%. Out of 59 Gram-positive cocci, the majority were *S. aureus* with 22.2% followed by *Coagulase negative Staphylococcus* with 11.7% and *Enterococcus* species as 2.6%.

In the current study, among the isolated Gram-negative uropathogens, third generation Cephalosporins i.e., Ceftriaxone in *E. coli* and *K. pneumoniae* showed maximum resistance of 60% and 64%, respectively, followed by 50% in *A. baumannii*. 55% and 58% of isolates of *E. coli* and *K. pneumoniae* were resistant to Ciprofloxacin. Maximum resistance to Ciprofloxacin (62%) was seen in case of *A. baumannii*. A fairly good sensitivity was seen in case of Fosfomycin in all Gram-negative isolates of a minimum 93% as compared to Nitrofurantoin with 72% susceptibility. Furthermore, Tigecycline and Colistin also showed a good pattern of sensitivity (Fig. 3).

Similarly, among the isolated Gram-positive uropathogens, Penicillin's were the most resistant (60%) while Linezolid, Vancomycin, and Teicoplanin showed excellent sensitivity of 96%, 96%, and 97%, respectively. Fosfomycin showed excellent activity against both *S. aureus* (94%) and *Enterococcus* (100%) (Fig. 4).

Furthermore, on evaluation of ESBL production among the 405 isolates of Enterobacteriaceae family, 108/235(45.9%) of *E. coli*, 55/107(58.8%) of *K. pneumoniae*, 6/23(26%) of *Enterobacter aerogenes,* 2/27(7.4%), *Proteus* spp., and 2/13(15.3%) of *Citrobacter* spp., was ESBL producers. Fosfomycin depicted good *in vitro* activity against these ESBL producers as 106/108 (98.1%) of *E. coli*, 50/55 (90.9%) of *K. pneumoniae*, 5/6 (83.3%) of *E. aerogenes* and both the ESBL producing isolates of *Proteus* and *Citrobacter* were found susceptible to Fosfomycin (Fig. 5). Gopichand *et al.* [13], Bakshi *et al.* [14], and Anand *et al.* [15] noted 100% susceptibility of Fosfomycin among ESBL producing isolates.

MDR organisms are resistant to any three different classes of antibiotics as defined by the standard guidelines [2]. Similar observation was seen in various other studies where the prevalence of MDR isolates varied from 28.03% to 51.50% [14-17]. Another study from Pune, Dalai *et al*. [19] reported a low prevalence of 14.80%. These variations are due to the different antibiotic usage and infection control measures in hospitals of different geographical areas.

Acquired MBLs have recently emerged as one of the most worrisome resistance mechanisms due to their capacity to hydrolyze all β-lactams, including carbapenems. In the present study, non-fermenters i.e., *P. aeruginosa* and *A. baumannii* contributed to the maximum cases of MBL production (25%) followed by *K. pneumoniae* (18.7%), and *E. aerogenes* (17.3%) (Fig. 6). Tellis *et al*. [20] recorded almost similar findings with *P. aeruginosa*, MBL isolates as 20.8%. However dissimilar results were obtained by a study done by Kaur [21] that reported, 0% *E coli*, 75% *K. pneumoniae*, and 50 % isolates of *P. aeruginosa* as MBL producers. Due to the multipledrug-resistance conferred by MBLs, their detection and control of spread by following stringent infection control practices alongside proper therapeutic regimens in both community and healthcare setup is the need of the hour.

The notable finding in our study was 86.9% MDR isolates and 88.8% MBL producers of uropathogenic *E. coli* exhibited good *in vitro* activity toward Fosfomycin followed by 87.8% MDR and 80% MBL producers of *K. pneumoniae*. All MDR isolates of *Proteus* and *Citrobacter* spp. were susceptible to Fosfomycin (Fig. 7). In addition, even the MDR and MBL-producing strains of *P. aeruginosa* depicted 80% and 88.8% susceptibility toward Fosfomycin. In a study done by Sundaramurthy *et al*. [22] all the isolates of Escherichia coli including ESBL producers, Carbapenamase producers were found susceptible to fosfomycin. Sahni *et al*. [23] found susceptibility of 83.0% in their study, Jain *et al*. [18] depicted Fosfomycin susceptibility among MDR isolates as 84.82% which was concordant with the findings of Dalai *et al*. [19] and Sreenivasan *et al*. [1]. In a study conducted by Banerjee *et al*. [2], the susceptibility among carbapenem-resistant Enterobacteriaceae was also found to be quite high. Thus such high susceptibility of Fosfomycin can serve as a boon and can have an added advantage in clinical day-to-day practice over the most commonly prescribed nephrotoxic Polymyxins as the salvage therapy for these cases.

Limitations

The limitation of our study was lacking clinical information regarding symptomatic or asymptomatic UTI, complicated, or uncomplicated, and distribution of patients based on the sources of infection, such as Catheter-associated or Community-acquired UTI.

CONCLUSION

This study confirmed the high *in vitro* susceptibility of Fosfomycin against both susceptible and MDR uropathogens including the ESBL and MBL producers. In the era of increasing antimicrobial resistance, Fosfomycin has the potential to emerge as an effective oral agent and a safe therapeutic option for empirical as well as definitive treatment of UTI in both community and healthcare setups. Moreover, it's easy dosage and compliance, minimal toxicity with negligible cross-resistance to other antibiotics are the additional advantages leading to the regaining of its antibacterial activity against bacterial pathogens.

AUTHORS CONTRIBUTION

Jasleen Kaur has prepared, reviewed, and supervised the manuscript. Priya Bhat has prepared and reviewed the manuscript, and Upasana Bhumbla is the corresponding author, who has reviewed and supervised the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

AUTHORS FUNDING

No funding was given.

REFERENCES

1. 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 Puducherry. J Lab Physicians. 2019;11:249-52. doi: 10.4103/JLP.JLP_27_19
2. Banerjee S, Sengupta M, Sarker TK. Fosfomycin susceptibility among multidrug-resistant, extended-spectrum beta-lactamase-producing, carbapenem-resistant uropathogens. Indian J Urol. 2017;33:149-54. doi: 10.4103/iju.IJU_285_16
3. Kothari A, Chaturvedi P, Bhumbla U. Fosfomycin susceptibility among multidrug-resistant extended-spectrum beta-lactamase and metallo-beta lactamase-producing uropathogens in a tertiary care hospital. Infect Dis Clin Pract. 2024;32:e1348. doi: 10.1097/IPC.0000000000001348
4. Procop GW, Church DL, Hall GS, Janda WM. Koneman's Color

Atlas and Textbook of Diagnostic. Philadelphia, PA: Wolters Kluwer Health; 2017.
5. Palzkill T. Metallo-β-lactamase structure and function. Ann N Y Acad Sci. 2013;1277:91-104. doi: 10.1111/j.1749-6632.2012.06796.x
6. Karageorgopoulos DE, Wang R, Yu XH, Falagas ME. Fosfomycin: Evaluation of the published evidence on the emergence of antimicrobial resistance in gram-negative pathogens. J Antimicrob Chemother. 2012;67(2):255-68. doi: 10.1093/jac/dkr466
7. Mothibi LM, Bosman NN, Nana T. Fosfomycin susceptibility of uropathogens at Charlotte Maxeke Johannesburg Academic Hospital. S Afr J Infect Dis. 2020;35(1):a173. doi: 10.4102/sajid.v35i1.173
8. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 32nd ed. CLSI Supplement M100. United States: Clinical and Laboratory Standards Institute; 2022
9. Sharmin S, Mostofa Kamal SM, Reza MA, Ashik Elahi KM, Mostofa Elma SM, Habib B. Fosfomycin-a promising oral antibiotic for the treatment of Urinary Tract Infection (UTI). Open J Urol. 2022;12:257-70. doi: 10.4236/oju.2022.125026
10. Singh MM, Devi R, Garg S, Mehra M. Effectiveness of syndromic approach in management of reproductive tract infections in Women. Indian J Med Sci. 2001;55:209-14.
11. Sood S, Gupta R. Antibiotic resistance pattern of community acquired uropathogens at a tertiary care hospital in Jaipur, Rajasthan. Indian J Community Med. 2012;37:39-44. doi: 10.4103/0970-0218.94023
12. Sharlee R, Sumangala B. Fosfomycin susceptibility on uropathogens in a tertiary care hospital, Mandya institute of medical sciences, Mandya. Indian J Microbiol Res. 2019;6(1):15-17. doi: 10.18231/2394-5478.2019.0004
13. Gopichand P, Agarwal G, Natarajan M, Mandal J, Deepanjali S, Parameswaran S, *et al. In vitro* effect of fosfomycin on multi-drug resistant gram-negative bacteria causing urinary tract infections. Infect Drug Resist. 2019;12:2005-13. doi: 10.2147/IDR.S207569
14. Bakshi R, Sehgal VK, Kansal P, Kaur S. Detection of extended-spectrum beta lactamases and AmpC beta lactamases producing uropathogenic *Escherichia coli* in a tertiary care hospital. Int J Med Dent Sci. 2019;8:1783-92. doi: 10.18311/ijmds/2019/23503
15. Anand M, Sahu C, Negi P, Singh A. *In vitro* assessment of fosfomycin: A beacon of hope in drug resistant organisms causing urinary tract infections. J Adv Med Med Res. 2019;30:1-9. doi: 10.9734/jammr/2019/v30i230169
16. Das B, Mittal N, Goswami R, Adhana D, Rathore N. Prevalence of Multidrug Resistance (MDR) and Extended Spectrum Beta-lactamases (ESBLs) among uropathogenic *Escherichia coli* isolates from female patients in a tertiary care hospital in North India. Int J Reprod Contracept Obstet Gynecol. 2018;7:5031-6. doi: 10.18203/2320-1770.ijrcog20184961
17. Asha Pai KB, Rajagopalan B. Susceptibility of urinary *Escherichia coli* to fosfomycin and nitrofurantoin-re-exploration of old and forgotten oral antibiotics. J Evol Med Dent Sci. 2020;9:928-31. doi: 10.14260/jemds/2020/200
18. Jain R, Pal N, Hooja S. Fosfomycin susceptibility among multidrug resistant and extended spectrum β-lactamase producing uropathogenic *Escherichia coli* isolates at a tertiary care hospital of Western India. CHRISMED J Health Res. 2022;9:125-9. doi: 10.4103/cjhr.cjhr_21_21
19. Dalai S, Modak M, Lahiri K. Fosfomycin susceptibility among uropathogenic *E. coli* and *K. pneumoniae*. Int J Sci Res. 2019;8:282-4.
20. Tellis RC, Moosabba MS, Roche RA. Correlation between biofilm formation and antibiotic resistance in uropathogenic *Pseudomonas aeruginosa* Causing catheter associated urinary tract infections. Eur J Pharm Med Res. 2017;4:248-52.
21. Kaur DC. Prevalence of metallo-β-lactamase in gram negative uropathogens from a tertiary care rural hospital. Dent Hist. 2015;17(67):11-5.
22. Sundaramurthy R, Tiruvanamalai R, Sivaraman ST, Arunagiri R, Charles J. Study on clinico microbiological profile and antibiotic susceptibility pattern of urinary tract pathogens with special reference to susceptibility of *Escherichia coli* to fosfomycin. Indian J Microbiol Res. 2018;5:258-66. doi: 10.18231/2394-5478.2018.0054
23. Sahni RD, Balaji V, Varghese R, John J, Tansarli GS, Falagas ME. Evaluation of fosfomycin activity against uropathogens in a fosfomycin-naive population in South India: A prospective study. Future Microbiol. 2013;8:675-80. doi: 10.2217/fmb.13.31