



## EMERGING BURDEN OF FOSFOMYCIN RESISTANCE AMONG UROPATHOGENIC ESCHERICHIA COLI ISOLATES: A GROWING THERAPEUTIC CONCERN

### Clinical Microbiology

<b>Dr. Daya Katariya</b>	Consultant Microbiologist, Desai Metropolis Health Services Pvt. Ltd, Surat, Gujarat, India
<b>Dr. Priyanka Parmar*</b>	Assistant Professor, Department of Microbiology, Ananya college of medicine and research, kalol, Gujarat, india*Corresponding Author
<b>Dr. Pranav Desa</b>	Chief of lab, Desai Metropolis Health Services Pvt. Ltd, Surat, Gujarat, India

### ABSTRACT

**Introduction:** Urinary tract infections (UTIs) are one of the most common conditions associated with significant morbidity and mortality. *Escherichia coli* (*E. coli*) are the main causative agent of UTIs. Most patients with uncomplicated UTIs are treated with empirical antibiotics without culture and a single oral dose of 3 g Fosfomycin is recommended for the treatment because of its broad-spectrum bactericidal activity. **Aim:** To evaluate the prevalence of fosfomycin resistance in urinary *E. coli* isolates. **Materials and Methods:** It is a retrospective cross-sectional study conducted over a period of 18 months (AUG-2024 to JAN-2026). We received Urine sample in sterile universal containers after that microscopic examination and culture has been done. Final identification & Antibiotic susceptibility testing was performed using the VITEK® 2 Compact system. **Results:** Out of 7056 urine samples, 2617 were culture- positive, with most common isolate is *E. coli* accounting for 1604 (61%), with lowest resistance in Colistin (0.31%) followed by Fosfomycin (0.62%) and Nitrofurantoin (6.48%). **Conclusions:** Being cheap, effective and high susceptibility rate fosfomycin is best first-line oral empiric antimicrobial drug for treating UTIs caused by *E. coli*.

### KEYWORDS

Urinary tract infections, *Escherichia coli*, Fosfomycin resistance.

### INTRODUCTION

Urinary tract infections (UTIs) are one of the most common conditions associated with significant morbidity and mortality in all age group with around 50% of women have experienced at least one UTI episode in their lifetime.<sup>1,2,3</sup>

UTIs are broadly classified in two main group community-acquired and hospital-acquired other one is uncomplicated and complicated.<sup>1</sup> Most UTI conditions are considered to be uncomplicated UTIs, defined as cystitis in a healthy person without relevant functional or anatomical abnormalities.<sup>1</sup> In contrast, complicated UTIs occur in people with kidney stones, blockages in the urinary tract, urine retention due to nerve damage, weakened immune systems, pregnancy or the presence of medical devices like catheters.<sup>3</sup> Among a wide array of gram positive, gram negative pathogens and certain fungi which are responsible for causing UTI, uropathogenic *Escherichia coli* (*E. coli*) is the main causative agent of uncomplicated (acute cystitis) and complicated (pyelonephritis) conditions.<sup>2,3,4</sup> Most patients with uncomplicated UTIs are treated with empirical antibiotics without culture, but it is recommended to treat UTIs empirically and send urine culture & sensitivity testing for later antimicrobial adjustment if the clinical condition does not improve.<sup>1,8</sup> A 2010 guideline from the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases recommends extended-release nitrofurantoin for five days, fosfomycin in a single dose, and trimethoprim or trimethoprim/sulfamethoxazole (COT) for three days as first-line treatment options<sup>6</sup> However, COT is recommended only if local resistance is less than 20%.<sup>6</sup>

Fosfomycin is a phosphonic acid derivative discovered in Spain in 1969, have a broad-spectrum bactericidal activity has emerged as one of the most active drugs for uncomplicated UTIs.<sup>2,4,7</sup> A single oral dose of 3 g Fosfomycin is recommended for the treatment, which maintain high concentrations in the urinary tract for 24 hours with minimal side effects and limited adverse effect.<sup>2,4,5</sup> Fosfomycin is an inhibitor of the MurA enzyme, UDP-N-acetylglucosamine enolpyruvyl transferase; thus, it inhibits the synthesis of peptidoglycan, which is necessary for bacterial cell wall synthesis. Because of this unique structure and action mechanism cross-resistance is rare.<sup>5</sup> ESBL- producing Enterobacteriaceae are frequently exposed to broad spectrum antibiotics, which may responsible for resistance to fosfomycin.<sup>2</sup> Other resistance mechanism have been reported in *E. coli* such as chromosomal mutations in the target gene (*murA*) or in fosfomycin transporter genes (*glpT* and *uhpT*), and the acquisition of plasmid-mediated fos genes that inactivate fosfomycin.<sup>7</sup>

Aim of this study is to evaluate the prevalence of fosfomycin resistance

in urinary *E. coli* isolates which, might be differ with demographic factors (age and gender). This will helps to guide the clinician in selecting fosfomycin as an empiric treatment of UTIs.

### Materials and Methods

It is a retrospective cross-sectional study conducted in Microbiology laboratory at Desai Metropolis Health Service Private Limited, Surat over a period of 18 months (starting from AUG-2024 to JAN-2026). Data was collected from the computerized database of the laboratory and analysed. The study includes all the non-duplicate *E. coli* strains isolated from urine samples received in the laboratory with clinical suspicion of UTI.

### Laboratory procedure

Urine sample was collected in sterile universal containers, with standard protocol and transported it to the laboratory without delay. If there were delays for more than 1–2 h, samples were stored in a refrigerator at 4 °C or transported in a refrigerated container.

Urine was microscopically examined through wet mount preparation to detect the presence of pus cells, red blood cells, casts and epithelial cells. Urine culture was done by semi-quantitative method using a standard calibrated nichrome loop (4 mm internal diameter of a standard loop is equal to 0.01 ml), a loopful well mixed uncentrifuged urine was inoculated on Nutrient agar & MacConkey agar and incubated for 24-48 hours at 37°C aerobically to check for the bacterial growth. For interpretation of significant bacteriuria we followed the Kass criteria, according to that colony count  $\geq 10^5$  CFU/mL considered as significant growth.<sup>2</sup> If a urine specimen grew > 2 organisms, it was considered as contaminated and was excluded from the study. Culture showing bacterial growth were analysed on the basis of colony characteristics and gram staining. Final identification & Antibiotic susceptibility testing (AST) was performed using the VITEK® 2 Compact system (bioMérieux, France) with the GN- 405 card, following the manufacturer's guidelines, but nitrofurantoin susceptibility in gram negative bacteria was done on Mueller Hinton Agar by Kirby Bauer disc diffusion method separately. AST data including minimum inhibitory concentration (MIC) and/or categorial interpretation of antimicrobial testing (S/I/R) had done according to the Clinical and Laboratory Standards Institute (CLSI) guidelines for that specific year.<sup>10,11</sup>

The data were entered in MS Excel and applicable statically analysis was done. Data were expressed in terms of frequency and percentage.

### RESULTS

Out of the 7056 urine samples were received in Microbiology

laboratory, 2617 exhibited clinically significant growth. The gender distribution showed that male: female ratio was around 1:3. Regarding the age group, more than half of the patients belonged to the age group of 21-60 years, followed by patients above 60 years of age. Table 1 presents a summary of the parameters of study.

**Table 1:** Summary of different parameters of study

Parameter		Value
Total Urine Sample received		7056
Total significant growth		2617
Gender	Male	2543 (36%)
	Female	4513 (63%)
Age group (in years)	<1	72
	1-20	485
	21-59	3633
	>60	2866

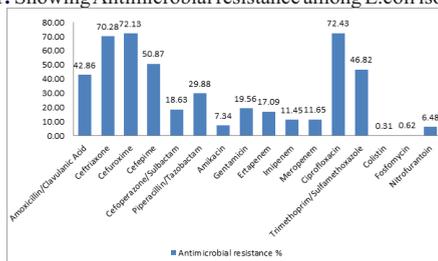
Among the culture positive samples (2617), the predominant uropathogens included *E. coli* (61%), followed by *K. pneumoniae* (18%) as shown in Table 2.

**Table 2:** Summary of organisms isolated from urine

Organisms Isolated	No. (%)
<i>E. coli</i>	1604 (61)
<i>Klebsiella spp.</i>	478 (18)
<i>Pseudomonas aeruginosa</i>	104 (4)
<i>Citrobacter spp</i>	48 (2)
<i>Enterobacter cloacae</i>	54 (2)
<i>Proteus spp</i>	35 (1)
<i>Enterococcus spp</i>	86 (3)
<i>Staphylococcus spp</i>	24 (1)
<i>Candida spp</i>	184 (7)

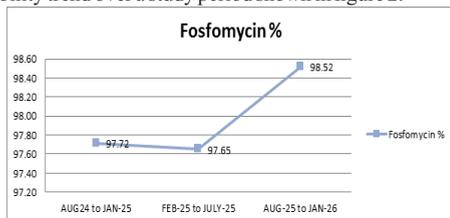
Figure 1 shows that lower rates of resistance were observed for Colistin (0.31%), Fosfomycin (0.62%), Nitrofurantoin (6.48%) and Amikacin (7.34%) in *Escherichia coli*. The maximum resistance was seen for Ciprofloxacin (72.43%), followed by Cefuroxime (72.13%) and ceftriaxone (70.28%).

**Figure 1:** Showing Antimicrobial resistance among *E. coli* isolates



**Figure 1:** Showing Antimicrobial resistance among *E. coli* isolates

Overall, fosfomycin, nitrofurantoin and colistin showed relatively lower resistance against *E. coli*. In vitro fosfomycin susceptibility was 97.95% followed by nitrofurantoin (90.71%). Fosfomycin susceptibility trend over a study period shown in figure 2.



**Figure 2:** Half yearly Fosfomycin susceptibility %

Thus, our study suggests that fosfomycin should be preferred over nitrofurantoin, fluoroquinolones or cotrimoxazole as a first-line agent for the treatment of uncomplicated UTI. Colistin should be spared as a last resort of treatment.

**DISCUSSION**

There is increased in resistance to regularly used antibiotics is a serious public health threat. Thus, adapting appropriate antibiotic dosage

guidelines based on regional surveillance or study is essential. Similar to earlier studies, the majority of the participants in our research were females (63%).<sup>1,2,5</sup> This could be attributed to the shorter urethra and the close proximity of urethral meatus to anus in females leading to increased chances of UTI in females. Our study results showed that the majority of patients were adults (Age group 21-59yr), which is consistent with a study conducted by Kazmi SY et al.1 In our study *E. coli* (61%) is most commonly isolated uropathogen, followed by *Klebsiella spp* (18%). *E. coli* is the most common uropathogen similar to several different studies.<sup>1,2,3,8,5</sup>

In our study resistance of antibiotics are as follows, Colistin (0.31%), Fosfomycin (0.62%), Nitrofurantoin (6.48%), Amikacin (7.34%), Trimethoprim/Sulfamethoxazole (46.82%), Ceftriaxone (70.28%), Cefuroxime (72.13%), Ciprofloxacin (72.43%). Contrary to our study, Kazmi SY et al.1 study shows high resistance in fosfomycin (33%) and nitrofurantoin (28%) but resistance of trimethoprim/sulfamethoxazole is 43% which quite similar to our study. Furthermore, similar to our study Colistin also showed a good pattern of sensitivity.<sup>2</sup> Similar to our study, Tanrıverdi-Çaycı Y et al.5 study showed fosfomycin resistance of *E. coli* as 1.98%. In study conducted by Hidalgo E et al.9 Susceptibility to fosfomycin in *E. coli* has been higher than 95% throughout the years same as our study.

**CONCLUSIONS**

Through our study, we can confirm that fosfomycin has high in vitro susceptibility. It is the best first-line oral empiric antimicrobial drug for effectively treating UTIs caused by *E. coli*. Trimethoprim sulfamethoxazole and ciprofloxacin should not recommend as first-line empiric drugs to treat UTI.

**REFERENCES**

- Kazmi SY, Fathima K, Khan N, Kulsum SN, Faraz A. Sensitivity Profile of Fosfomycin, Nitrofurantoin, and Co-trimoxazole Against Uropathogens Isolated From UTI Cases in a Secondary Care Center, KSA. *Cureus*. 2024 Feb 11;16(2):e53999. doi: 10.7759/cureus.53999. PMID: 38476810; PMCID: PMC10928802.
- Kaur J, Bhat P, Bhumbra U. Fosfomycin susceptibility in multidrug resistant uropathogens: A retrospective study in the era of antimicrobial resistance. *J Family Med Prim Care*. 2025 Apr;14(4):1346-1351. doi: 10.4103/jfmpc.jfmpc\_1074\_24. Epub 2025 Apr 25. PMID: 40396075; PMCID: PMC12088565.
- Thakur P, Kaur N, Chauhan S, Abdelmonem R, Amponsah RD. Fosfomycin resistance in extended-spectrum beta-lactamase producing *Escherichia coli* isolated from urinary tract-infected patients in a tertiary care hospital. *J Med Microbiol*. 2025 Jul;74(7):002039. doi: 10.1099/jmm.0.002039. Erratum in: *J Med Microbiol*. 2025 Sep;74(9). doi: 10.1099/jmm.0.002076. PMID: 40658603; PMCID: PMC12306686.
- Ribeiro VST, Bail L, Ito CAS, Andrade AP, Arend LNV, Suss PH, Nogueira KDS, Wallfor HSM, Faoro H, Kuczera LCSM, Vicenzi FJ, Tuon FF. In vitro susceptibility to fosfomycin in clinical and environmental extended-spectrum beta-lactamase producing and/or ciprofloxacin-non-susceptible *Escherichia coli* isolates. *Rev Inst Med Trop Sao Paulo*. 2024 Feb 5;66:e5. doi: 10.1590/S1678-9946202466005. PMID: 38324871; PMCID: PMC10846478.
- Tanrıverdi-Çaycı Y, Güne DB, Ertokatlı M, Hacıteminoğlu-Ülker K, Birinci A. Prevalence of Fosfomycin Resistance Among Enterobacterales Isolates in A Tertiary Care Hospital from Turkey. *Infect Dis Clin Microbiol*. 2022 Dec 21;4(4):252-257. doi: 10.36519/idem.2022.163. PMID: 38633718; PMCID: PMC10985827.
- Kurotschka PK, Gágyor I, Ebell MH. Acute Uncomplicated UTIs in Adults: Rapid Evidence Review. *Am Fam Physician*. 2024 Feb;109(2):167-174. PMID: 38393801.
- Ríos, E., del Carmen López Díaz, M., Culebras, E. et al. Resistance to fosfomycin is increasing and is significantly associated with extended-spectrum β-lactamase-production in urinary isolates of *Escherichia coli*. *Med Microbiol Immunol* 211, 269–272 (2022). <https://doi.org/10.1007/s00430-022-00749-2>
- Batra P, Abrol AK, Gupta S, Pushpan P, Kumar R. Susceptibility pattern of oral antimicrobials in uncomplicated UTI: Does fosfomycin still stand effective? *J Family Med Prim Care*. 2020 Feb 28;9(2):850-853. doi: 10.4103/jfmpc.jfmpc\_970\_19. PMID: 32318433; PMCID: PMC7113987.
- Hidalgo E, González-Torralba A, Ramón J, Alós JI. Maintained susceptibility to fosfomycin in extra-hospitalary urinary isolates of *Escherichia coli*. Strong association of fosfomycin resistance with age and ESBL production. *Rev Esp Quimioter*. 2025 Feb;38(1):55-58. doi: 10.37201/req/016.2024. Epub 2024 Dec 20. PMID: 39704031; PMCID: PMC11758869.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 35th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2025