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

Clinical Microbiology

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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.[1,2,3]

UTIs are broadly classified in two main group community-acquired and hospital-acquired other one is uncomplicated and complicated.[1] Most UTI conditions are considered to be uncomplicated UTIs, defined as cystitis in a healthy person without relevant functional or anatomical abnormalities.[1] 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.[3] 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.[2,3,4] 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.[1,8] 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[6] However, COT is recommended only if local resistance is less than 20%.[6]

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.[2,4,7] 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.[2,4,5] 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.[5] ESBL- producing Enterobacteriaceae are frequently exposed to broad spectrum antibiotics, which may responsible for resistance to fosfomycin.[5] 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.[7]

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.[2] 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.[10,11]

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. (%)
E.coli	1604 (61)
Klebsiella spp.	478 (18)
Pseudomonas aeruginosa	104 (4)
Citrobacter spp	48 (2)
Enterobacter cloacae	54 (2)
Proteus spp	35 (1)
Enterococcus spp	86 (3)
Staphylococcus spp	24 (1)
Candida spp	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

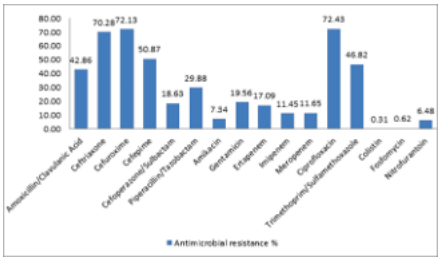

Figure 1: Showing Antimicrobial resistance among E.coli isolates

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.

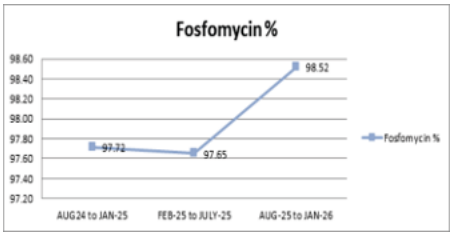

Figure 2: Half yearly Fosfomycin susceptibility %

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%).[1,2,5] 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.[1,2,3,8,5]

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.2 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.

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