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# Evaluating The Role of Fosfomycin in Treating MDR Urinary Pathogens: A Tertiary Care Hospital Perspective

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## Abstract

**Urinary tract infections (UTIs) are most common infections encountered in both community and hospital settings and are frequently treated with antibiotics. *Escherichia coli* and *Klebsiella pneumoniae*, members of the *Enterobacteriaceae* family, are the predominant uropathogens. The rise of resistant uropathogens, that exhibit significant rates of antibiotic resistance, is making therapy more demanding. Increasing usage of carbapenem in complicated urinary infections is resulting in the Carbapenem-resistant escalation property in the gram-negative bacilli. This research was done to assess *in vitro* susceptibility of fosfomycin against both uropathogenic *E. coli* and *K. pneumoniae*. Over an interval of three months, 1070 urine samples were processed (January to March 2024). After an exclusion criteria, 1000 Specimens were inoculated on blood and Macconkey agar and incubated at 37 °C. Microbial growth and colony counts were noted. Speciation and antibiotic sensitivity pattern were analysed using Automated compact system of VITEK 2 (BioMerieux Inc., France). Fosfomycin discs were used to determine CRE and ESBL producers. Overall, 99.43% of *E. coli* isolates were susceptible to fosfomycin. *E. coli* that produce carbapenemase and ESBL had a fosfomycin susceptibility of 99.17% and 98.78%, respectively. The overall fosfomycin susceptibility of *K. pneumoniae* is 91.30%. Fosfomycin is effective against 91.6% and 87.5% of the carbapenem-resistant and ESBL-producing strains of *K. pneumoniae*, respectively. Although fosfomycin resistance is currently low, it may be a therapeutic alternative relative to other medications used for the management of UTIS caused by ESBL and carbapenem-resistant *E. coli* and *K. pneumoniae*. To preserve the efficacy of fosfomycin it must be used carefully following antimicrobial stewardship principles and guidelines.**

**Keywords:** *E. coli*, *Klebsiella* spp., Fosfomycin, ESBL, CRE

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## INTRODUCTION

Urinary tract infections (UTIs) are among the most common infections encountered in both community and healthcare settings and frequently require antibiotic treatment.[1] The most often reported agents are gram-negative bacteria belonging to the *Enterobacteriaceae* family, specifically *Escherichia coli* and *Klebsiella pneumoniae.*[2] The uropathogens that Produce Extended-spectrum beta-Lactamases (ESBLs), shows significant antibiotic resistance, which makes therapy more complicated.[3] Increased utilization of carbapenem drugs in complicated urinary tract infections leads to the development of carbapenem drug-resistance in gram-negative bacilli. Organisms that exhibit resistance for at least three antibiotic classes are referred to as multidrug-resistant organism (MDRO).[4] Treating infections caused by ESBL-producing strains often necessitates alternative agents, including aminoglycosides, newer beta-lactam/beta-lactamase inhibitor combinations, carbapenems, fosfomycin, and agents like piperacillin/tazobactam or cefoperazone/tazobactam.

Fosfomycin, a broad-spectrum antibiotic is administered in the form of fosfomycin tromethamine, inhibits bacterial cell wall formation by interferes peptidoglycan synthesis for the treating of mild to severe infections of urinary tract caused by the organisms that are susceptible.[5-8] Fosfomycin is a broad-spectrum antibiotic that is administered orally and excreted in the urine with high concentrations up to 24 hours, making it highly efficient against uropathogenic organisms.[9,10] Due to its unique chemical structure, mechanism of action and low chromosomal mutations which do not spread rapidly, maintain a low fosfomycin resistance rate. All the systematic reviews and Meta analysis showed that single dosage of fosfomycin was effective as longer courses of alternate antibiotics agents for treating uncomplicated UTI.[11]

New antibiotics, antimicrobial resistance profiles must be updated on a regular basis, to guide appropriate antibiotic stewardship measures. This study set out to examine of fosfomycin *in vitro* susceptibility against both uropathogenic MDR *E. coli* and *K. pneumoniae*, as there haven't been many studies done in this area. The objective was to evaluate the potential choice of drug for treating UTIs caused due to Uropathogenic *E. coli* (UPEC) and *Klebsiella* species, evaluating its clinical efficacy and suitability.

## MATERIALS AND METHODS

A retrospective research was performed within the Microbiology Department, Saveetha Medical College, Thandalam, Chennai, Tamil Nadu, India, over a period of 3 months from January 2024 to March 2024.

### Inclusion criteria

Urine samples were collected from symptomatic persons. Single sample per subject was included in the study.

### Exclusion criteria

Samples were excluded if the individuals were on antibiotic treatment, as well as those who underwent recurrent sampling.

### Processing of urine samples

In the course of three months, 1070 urine samples were processed from January to March 2024. After applying the exclusion criteria, 70 samples were excluded-45 due to recent antibiotic use and 25 due to duplicate submissions-resulting in 1,000 samples included in the final analysis. These specimens were cultured onto routine culture media and held at 37 °C for a duration of 18 to 24 hours. After incubation, growth was evaluated. A pure bacterial growth culture with a colony count greater than $10^5$ CFU/ml is considered significant bacteriuria. Standard microbiological techniques were employed to determine the growth of each sample.[12]

### Detection and Characterization of urinary isolates

After acquiring the pure growth of bacterial culture, antibiotic susceptibility was further identified and determined by automated VITEK 2 compact system (BioMerieux SA). For Identification of isolates GN ID and AST cards were used, especially the AST405 card for fermenter bacteria and the AST 407 card for critical care patients. A quantitative measurement of growth was carried out using an optical reader.[13] Simultaneously antimicrobial susceptibility test of

these culture-positive isolates were determined by using the Kirby Bauer disc diffusion method by inoculating on MHA plate after adjusting the turbidity to 0.5 McFarlands.[14] Fosfomycin disks (HiMedia Laboratories Pvt. Limited, India), 200 µg comprising 50 µg of glucose-6 phosphate are inserted. Incubated the culture Plates at 37 °C for 24 hrs. The zone of inhibition and its diameter were measured. *E. coli* ATCC 25922, ATCC 35218 and *K. pneumoniae* ATCC 13883 were served as a reference strains.

Out of the 1000 specimens, 222 (22.2%) non-duplicated uropathogenic *Enterobacteriaceae* were isolated. The uropathogenic multidrug-resistant organisms isolated were confirmed by VITEK 2 Advanced expert system (AES) as Phenotypes flagged ESBL, CRE producing phenotypes.[15,16]

### Statistics

The fosfomycin susceptible uropathogenic organisms were calculated by using descriptive statistics.

## RESULTS

The study analyzed 1000 urine samples. Among these, 222 (20.74%) non-duplicated uropathogenic *Enterobacteriaceae* were isolated (Table 1). Out of these isolates, 176 (79.27%) were *E. coli* and 46 (20.72%) were *Klebsiella* species. Among the 176 *E. coli* isolates, 121 (68.75%) are ESBL producers, 55 (31.25%) are non-ESBL producers. Additionally, 82 (46.59%) were carbapenem-resistant *E. coli* (CRE), while 94 (53.4%) were non-carbapenem-resistant (non-CRE). Among the 46 isolates of *Klebsiella* species, 36 (78.26%) were found to produce ESBL, and 10 (21.73%) were non-ESBL producers. Furthermore, 16 (34.78%) were carbapenem-resistant strains (CRS), while 30 (65.21%) were non-carbapenem-resistant *Klebsiella* species, as illustrated in Figure 1.

*E. coli's* overall susceptibility to fosfomycin is 175 (99.4%). While 98.78% of bacteria are resistant to carbapenems. 99.17% of ESBL-producing *E. coli* are susceptible to fosfomycin (Table 2 and 3).

**Table 1.** Total number of *Enterobacteriaceae* isolates showing ESBL, Non-ESBL and CRE, Non-CRE producers

| Organisms | Total (n%) | ESBL (n%) | Non-ESBL (n%) | CRE (n%) | Non-CRE (n%) |
|---|---|---|---|---|---|
| *E. coli* | 176 (79.2%) | 121 (68.75%) | 55 (31.25%) | 82 (46.59%) | 94 (53.40%) |
| *K. pneumoniae* | 46 (20.7%) | 36 (78.26%) | 10 (21.73%) | 16 (34.78%) | 30 (65.21%) |

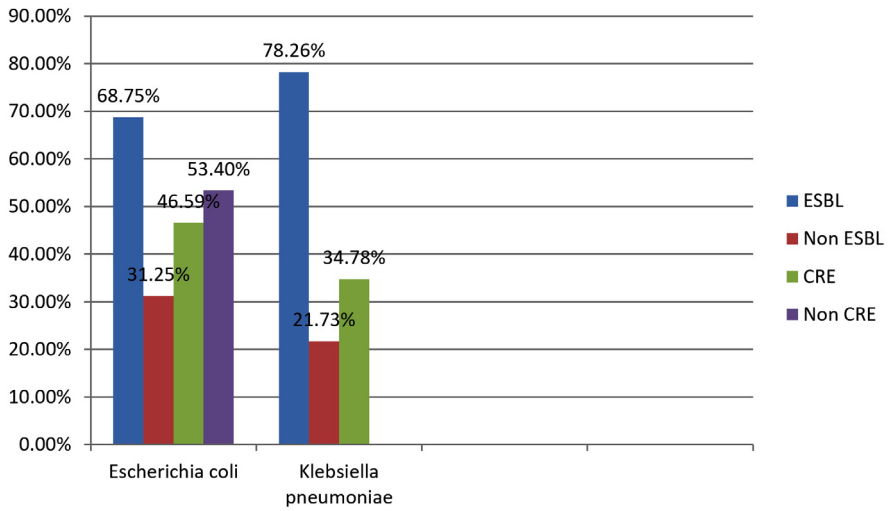


**Figure 1**. Total isolates of ESBL, Non-ESBL and CRE, Non-CRE producing *Enterobacteriaceae*

The overall susceptibility of fosfomycin among *K. pneumoniae* is 42 (91.30%) in ESBL-producing strains and 43 (93.4%) in carbapenem-resistant strains (CRE) of *Klebsiella* spp.

The ESBL-producing *K. pneumoniae* susceptible to fosfomycin was seen in 33 (91.6%), while among carbapenem-resistant strains, it was found in 14 (87.5%).

Significant differences were not found between susceptibility patterns of fosfomycin determined by the automated VITEK 2 compact system and manually used disc diffusion method (Figure 2 and 3).

## DISCUSSION

The rise in drug-resistance in the uropathogenic organisms including *K. pneumoniae* and *E. coli* constitute a increasing risk to the effective management of UTIs. The production of extended-spectrum β-lactamases (ESBLs) and carbapenemases limit the therapeutic options available and contribute to treatment failures and disease recurrence.[17]

Drug fosfomycin originally known as phosphonomycin, this compound has wide range of antibacterial activity that was accidentally discovered in the fermentation broth *Streptomyces fradiae* in 1969.[18] Fosfomycin inhibits the pyruvyl transferase enzyme, which is essential for producing the precursors of peptidoglycan. Because fosfomycin interferes with the formation of peptidoglycan, an important component of bacterial cell walls, the bacteria cannot maintain the integrity of their cell walls, ultimately resulting in their death.[19]

**Table 2.** Fosfomycin susceptibility comparison in ESBL and Non-ESBL producers

| Organism Fosfomycin susceptibility (n%) | ESBL (n%) | Non-ESBL producers (n%) |
|---|---|---|
| *E. coli* (99.4%) | 120/121 (99.17%) | 55/55 (100%) |
| *Klebsiella pneumoniae* (91.3%) | 33/36 (91.6%) | 9/10 (90%) |
| Total | 153/157 (97.4%) | 64/65 (98.46%) |

**Table 3.** Fosfomycin susceptibility among Carbapenem-resistant and Non-carbapenem-resistant *Enterobacteriaceae*

| Organisms (n%) | CRE (n%) | Non-CRE (n%) |
|---|---|---|
| *E. coli* (99.4%) | 81/82 (98.7%) | 94/94 (100%) |
| *Klebsiella pneumoniae* (93.4%) | 14/16 (87.5%) | 29/30 (65.2%) |
| Total | 95/98 (96.9%) | 115/124 (92.7%) |

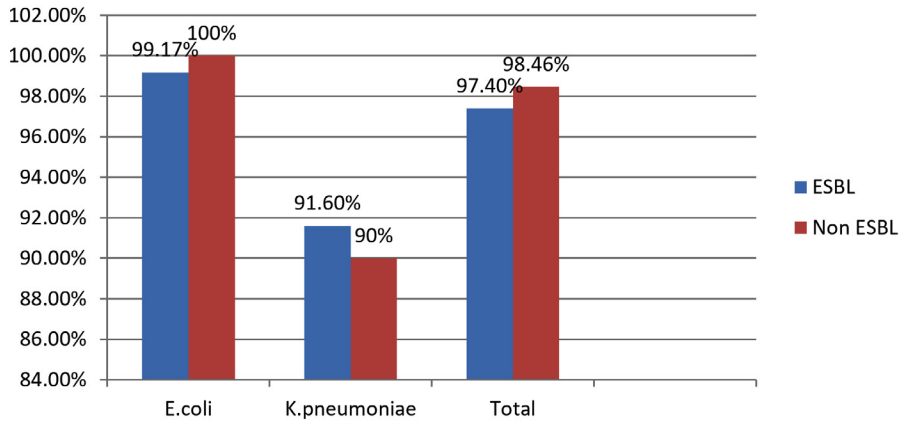


**Figure 2.** Fosfomycin susceptibility among ESBL and Non-ESBL producing *Enterobacteriaceae*

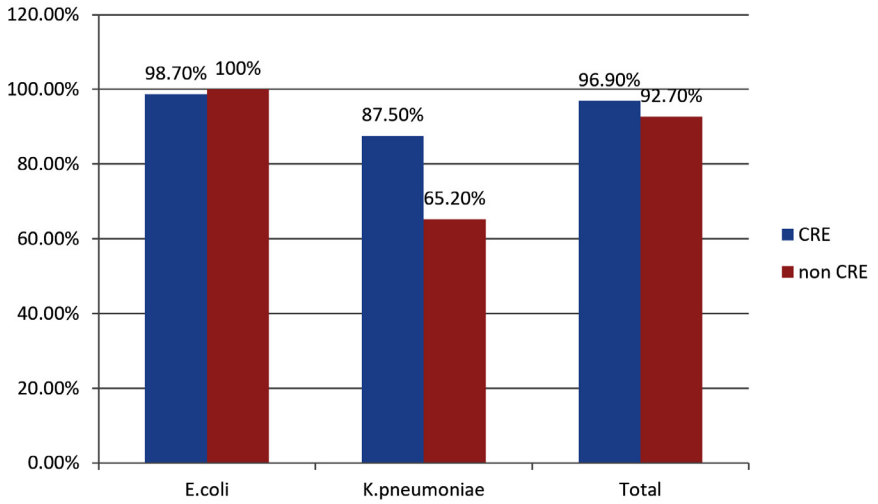


**Figure 3.** Fosfomycin susceptibility among Carbapenem-resistant and Non-carbapenem-resistant *Enterobacteriaceae*

In our study, we identified 176 isolates of *E. coli* out of 222 isolates and 46 isolates of *K. pneumoniae*. Among the 176 samples in which *E. coli* was isolated, 121 were found to produce ESBL, demonstrating sensitivity to fosfomycin at a rate of 99.1%, while 55 were non-ESBL producers, showing susceptibility to fosfomycin at 100%. Among the 82 carbapenem-resistant *E. coli*, 81 showed sensitivity to fosfomycin, while the remaining 94 noncarbapenem-resistant *E. coli* exhibited sensitivity. Similarly, 36 ESBL-producing *Klebsiella* spp. showed susceptibility to fosfomycin, while 16 carbapenem-resistant *Klebsiella* spp. showed susceptibility to fosfomycin.

In the AREC (Antimicrobial Resistance Epidemiological Survey on Cystitis) research group, 98.1% of *E. coli* isolated from urine samples were susceptible to fosfomycin,[20,21] which is quite similar to our data of 99.4%. Falgas *et al*. found that fosfomycin sensitivity was present in 97% of the ESBL-producing *E. coli* isolates.[11] Similarly, in research by Sardar *et al*., all isolates showed uniform sensitivity to fosfomycin (100%). which mirrored our findings.[21]

A study from the Netherlands has shown that the susceptibility rates for fosfomycin were 95.9% and 87.6% for *E. coli* and *K. pneumoniae*.[22] This includes overall vulnerability to ESBL and carbapenem-resistant strains of *E. coli* and *K. pneumoniae*.

Similar findings to ours were reported in India, Tulara *et al*.,[23] where it was reported that 99.6% of 384 ESBL-producing *E. coli* strains and 87.7% of 80 ESBL-producing *K. pneumoniae* strains were fosfomycin-sensitive.

In a study by Dalai and Modak *et al*.,[3] 96.8% of *E. coli* and 91.4% of *K. pneumoniae* were found to be susceptible to fosfomycin, indicating our data exhibit higher fosfomycin susceptibility against ESBL and carbapenemase producing uropathogenic *E. coli* and *K. pneumoniae*.

Fosfomycin has significant effectiveness against ESBL- and carbapenem-resistant *E. coli* and *K. pneumoniae*, making it a good choice for empirical therapy of urinary tract infections. Its oral bioavailability and broad-spectrum efficacy support its use in outpatient settings. Integrating fosfomycin into local therapy protocols may reduce dependency on carbapenems. This helps preserve last-line antibiotics and slow resistance development. Overall, fosfomycin supports both effective therapy and antimicrobial stewardship goals.

**Limitations**

The importance of the study was done to find the *in vitro* susceptibility of fosfomycin to *E. coli* and *K. pneumoniae* only. The present study included limited number of isolates, and the results obtained may not be generalizable to other

areas with different epidemiological antibiotic susceptibility patterns. Additionally, there was no MIC testing that might have yielded more accurate quantitative data about fosfomycin's activity. The study is also not designed to address clinical outcome, the follow-up of which was not included, and it was not possible to determine any association between *in vitro* susceptibility and patient response. In addition, genotyping of the mechanisms of resistance including ESBL or carbapenemase genes was not performed and this precludes an interpretation of the molecular mechanisms which underpin resistance.

## CONCLUSION

In conclusion, the study emphasizes the effectiveness of fosfomycin against uropathogenic ESBL-producers and carbapenem-resistant *E. coli* and *K. pneumoniae*. In comparison with other drugs, fosfomycin is a better therapeutic option for managing UTIs caused by ESBL and carbapenem-resistant *K. pneumoniae*, while current resistance to fosfomycin remains low. To preserve the efficacy of fosfomycin, it is crucial to ensure its prudent and appropriate use following antimicrobial stewardship principles and guidelines. Incorporating fosfomycin susceptibility tests into standard panels for multidrug-resistant (MDR) urinary tract infections (UTIs) may enhance the more precise and effective treatment recommendations.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## FUNDING

None.

## DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

## ETHICS STATEMENT

The study protocol was reviewed and approved by the Institutional Ethics Committee, Saveetha Medical College, vide approval no.: SMC/IEC/2024/156.

## INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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