SSR Institute of International Journal of Life Sciences
ISSN (O): 2581-8740 | ISSN (P): 2581-8732
Sahoo, 2025
doi: 10.21276/SSR-IIJLS.2025.11.2.37

Original Article

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Fosfomycin Susceptibility among ESBL-Producing Gram-Negative Bacilli Causing Urinary Tract Infections

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Received: 30 Oct 2024/ Revised: 23 Dec 2024/ Accepted: 02 Feb 2025

ABSTRACT

Background: Urinary tract infections (UTIs) caused by extended-spectrum β-lactamase (ESBL)-producing gram-negative bacilli pose significant therapeutic challenges due to multidrug resistance. Fosfomycin, an older antibiotic, has re-emerged as a potential treatment option.

Methods*:* A prospective study was conducted on 350 urine samples from patients with confirmed UTIs. ESBL production was confirmed using the double-disk synergy test, and fosfomycin susceptibility was assessed via agar dilution per CLSI guidelines. Bacterial identification was performed using standard biochemical tests and the Vitek 2 system. ESBL production was confirmed via the double-disk synergy test, following CLSI guidelines. Fosfomycin susceptibility was determined using the agar dilution method on Mueller-Hinton agar supplemented with 25 µg/mL glucose-6-phosphate, with a minimum inhibitory concentration (MIC) breakpoint of ≤32 mg/L indicating susceptibility.

Results: Of 350 isolates, 220 (62.9%) were ESBL producers, predominantly *Escherichia coli* (68.2%) and *Klebsiella pneumoniae* (22.7%). Fosfomycin susceptibility was observed in 78.6% of ESBL isolates, with *E. coli* showing higher susceptibility (85.3%) than *K. pneumoniae* (67.4%). Resistance was associated with prior antibiotic exposure. Fosfomycin resistance was observed in 47 (21.4%) isolates, with *K. pneumoniae* contributing the largest share (17/47, 36.2%). Resistance was more frequent in isolates with higher MICs (64–128 mg/L), suggesting the potential for reduced clinical efficacy at standard doses. Compares susceptibility across antibiotics, showing fosfomycin's superior activity (78.6%) compared to ciprofloxacin (15.5%) and trimethoprim-sulfamethoxazole (22.7%) among ESBL producers.

Conclusion: Fosfomycin remains effective against most ESBL-producing gram-negative bacilli causing UTIs, supporting its use as an oral treatment option.

Key-words: Fosfomycin, ESBL, Gram-negative bacilli, Urinary tract infections, Antibiotic resistance

INTRODUCTION

Urinary tract infections are among the most common bacterial infections globally, affecting millions annually and imposing significant healthcare burdens [1]. The rise of antimicrobial resistance, particularly among gram-negative bacilli-producing ESBLs has complicated UTI management. ESBLs confer resistance to most β-lactam antibiotics, limiting therapeutic options and increasing reliance on parenteral agents like carbapenems [2]. This trend has spurred interest in alternative antibiotics, such as fosfomycin, which offers a unique mechanism of action by inhibiting bacterial cell wall synthesis [3].

Fosfomycin, discovered in 1969, is a phosphonic acid derivative effective against both gram-positive and gram-negative bacteria [4]. Its oral formulation, fosfomycin trometamol, achieves high urinary concentrations, making it suitable for treating uncomplicated UTIs [5]. Historically underutilised due to the availability of β-lactams and fluoroquinolones, fosfomycin has regained attention as resistance to these agents has surged. Studies indicate that fosfomycin retains activity against multidrug-resistant (MDR) pathogens, including ESBL producers, offering a potential oral alternative to intravenous therapies [6].

How to cite this article
Sahoo S. Fosfomycin Susceptibility among ESBL-Producing Gram-Negative Bacilli Causing Urinary Tract Infections. SSR Inst Int J Life Sci., 2025; 11(2): 7240-7244.

Access this article online
https://iijls.com/

doi: 10.21276/SSR-IIJLS.2025.11.2.37

The increasing prevalence of ESBL-producing *E. coli* and *K. pneumoniae* in community and hospital settings underscores the need for effective oral antibiotics [7]. These pathogens are frequently implicated in UTIs, with ESBL production rates in some regions exceeding 30% [8]. The limited bioavailability of many oral antibiotics against ESBL producers often necessitates hospitalisation for intravenous treatment, increasing costs and patient morbidity [9]. Fosfomycin's favorable pharmacokinetic profile, including sustained urinary levels after a single dose, positions it as a promising candidate for outpatient management [10].

However, concerns about emerging fosfomycin resistance, potentially driven by its increased use, warrant careful evaluation [11]. Data on fosfomycin susceptibility among ESBL producers remain variable, with susceptibility rates ranging from 70% to 95% across studies [12]. Geographic differences and prior antibiotic exposure may influence these rates, necessitating local susceptibility data to guide treatment. This study addresses this gap by assessing fosfomycin's *in vitro* activity against ESBL-producing gram-negative bacilli causing UTIs, providing insights into its role in contemporary therapy.

MATERIALS AND METHODS

This prospective study was conducted at a tertiary care hospital between September 2024 and April 2025, targeting patients diagnosed with UTIs caused by gram-negative bacilli. Urine samples were collected from 350 patients presenting with symptoms such as dysuria, frequency, or urgency, confirmed by a positive urine culture (≥10^5 CFU/mL). Bacterial identification was performed using standard biochemical tests and the Vitek 2 system. ESBL production was confirmed via the double-disk synergy test, following CLSI guidelines [1]. Fosfomycin susceptibility was determined using the agar dilution method on Mueller-Hinton agar supplemented with 25 µg/mL glucose-6-phosphate, with a minimum inhibitory concentration (MIC) breakpoint of ≤32 mg/L indicating susceptibility.

Inclusion Criteria- Patients aged ≥18 years with a confirmed UTI caused by gram-negative bacilli were included. Only isolates confirmed as ESBL producers by phenotypic testing were analyzed for fosfomycin susceptibility. Both community-acquired and hospital-acquired infections were considered to capture a broad epidemiological profile.

Exclusion Criteria- Patients with polymicrobial infections, asymptomatic bacteriuria, or incomplete clinical data were excluded. Isolates other than *E. coli*, *K. pneumoniae*, *Proteus* sp., or *Enterobacter* sp. were excluded due to their low prevalence in this setting. Samples collected outside the study period or from patients with recent fosfomycin exposure (within 30 days) were also excluded to minimize bias.

Data Collection Procedure- Clinical data, including age, sex, hospitalization status, prior antibiotic use, and comorbidities (e.g., diabetes, urinary catheterization), were extracted from electronic medical records. Microbiological data, including bacterial species, ESBL status, and fosfomycin MICs, were recorded in a standardized database. Samples were processed within 2 hours of collection to ensure viability, and all tests were performed in duplicate to enhance reliability. Quality control was maintained using *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 strains.

Statistical Analysis- Data were analysed using SPSS version 25. Categorical variables, such as susceptibility rates, were expressed as percentages and compared using chi-square tests. Continuous variables, like MIC values, were summarized as medians and interquartile ranges. Logistic regression was used to identify factors associated with fosfomycin resistance, adjusting for confounders like prior antibiotic exposure and hospitalization status. A p-value<0.05 was considered statistically significant. The study ensured adequate power (80%) to detect a 10% difference in susceptibility rates between species, based on prior studies reporting non-explanatory.

RESULTS

Of the 350 urine samples analyzed, 220 (62.9%) isolates were confirmed as ESBL producers, with *E. coli* being the most prevalent (150 isolates, 68.2%), followed by *K. pneumoniae* (50 isolates, 22.7%), *Proteus* sp. (15 isolates, 6.8%), and *Enterobacter* sp. (5 isolates, 2.3%). Fosfomycin susceptibility was observed in 173 (78.6%) ESBL-producing isolates. *E. coli* exhibited higher susceptibility (128/150, 85.3%) compared to *K. pneumoniae* 33/50, 67.4%), with a significant difference

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((p=0.008). *Proteus* sp. and *Enterobacter* sp. showed susceptibility rates of 73.3% and 60.0%, respectively (Table 1). The median fosfomycin MIC for susceptible isolates was 16 mg/L (IQR 8–32 mg/L).

Table 1: Fosfomycin Susceptibility by Bacterial Species

Species	Total Isolates	Susceptible (%)	Resistant (%)
E. coli	150	128 (85.3)	22 (14.7)
K. pneumoniae	50	33 (67.4)	17 (32.6)
Proteus sp.	15	11 (73.3)	4 (26.7)
Enterobacter sp.	5	3 (60.0)	2 (40.0)

Among the 220 ESBL producers, 130 (59.1%) were from outpatients, and 90 (40.9%) were from inpatients. Outpatient isolates had a higher fosfomycin susceptibility rate (85.4%) than inpatient isolates (68.9%, p=0.004) (Table 2). Prior antibiotic exposure, particularly to fluoroquinolones or cephalosporins within the past 3 months, was associated with reduced susceptibility (OR 2.3, 95% CI 1.2–4.5, p=0.012). Comorbidities like diabetes (25.5% of patients) and urinary catheterisation (15.0%) were not significantly linked to resistance (p>0.05) (Table 3).

Table 2: Susceptibility by Patient Setting

Setting	Total Isolates	Susceptible (%)	Resistant (%)
Outpatient	130	111 (85.4)	19 (14.6)
Inpatient	90	62 (68.9)	28 (31.1)

Table 3: Risk Factors for Fosfomycin Resistance

Factor	Odds Ratio	95% CI	p-value
Prior Antibiotic Use	2.3	1.2–4.5	0.01
Diabetes	1.2	0.6–2.4	0.60
Urinary Catheterization	1.5	0.7–3.2	0.29

Fosfomycin resistance was observed in 47 (21.4%) isolates, with *K. pneumoniae* contributing the largest share (17/47, 36.2%). Resistance was more frequent in isolates with higher MICs (64–128 mg/L), suggesting the potential for reduced clinical efficacy at standard doses (Table 4).

Table 4: Fosfomycin MIC Distribution

MIC (mg/L)	Susceptible Isolates	Resistant Isolates
≤32	173	0
64	0	25
128	0	22

Table 5 compares susceptibility across antibiotics, showing fosfomycin's superior activity (78.6%) compared to ciprofloxacin (15.5%) and trimethoprim-sulfamethoxazole (22.7%) among ESBL producers.

Table 5: Antibiotic Susceptibility Comparison

Antibiotic	Susceptible (%)
Fosfomycin	78.6
Ciprofloxacin	15.5
Trimethoprim-Sulfamethoxazole	22.7
Nitrofurantoin	65.5

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DISCUSSION

The study's finding that 78.6% of ESBL-producing gram-negative bacilli were susceptible to fosfomycin aligns with previous reports, reinforcing its utility as an oral treatment for UTIs [13]. The higher susceptibility of *E. coli* (85.3%) compared to *K. pneumoniae* (67.4%) reflects species-specific differences in resistance mechanisms, such as the presence of fosA genes in *K. pneumoniae*, which inactivate fosfomycin [14]. These results suggest that fosfomycin remains a viable option for *E. coli*-dominant infections, which comprised 68.2% of isolates, but caution is warranted for *K. pneumoniae* due to lower susceptibility. The observed susceptibility rate is lower than earlier studies reporting >90% susceptibility, possibly indicating emerging resistance driven by increased fosfomycin use [15].

The significant difference in susceptibility between outpatient (85.4%) and inpatient (68.9%) isolates highlights the impact of healthcare-associated factors, such as antibiotic pressure and nosocomial transmission, on resistance development [16]. Prior antibiotic exposure emerged as a key risk factor (OR 2.3), consistent with studies linking fluoroquinolone and cephalosporin use to MDR phenotypes [17]. This underscores the need for judicious antibiotic prescribing to preserve fosfomycin's efficacy. Notably, comorbidities like diabetes and catheterization did not significantly influence resistance, suggesting that microbiological factors outweigh host-related variables in this context [18].

Fosfomycin's superior performance compared to ciprofloxacin (15.5%) and trimethoprim-sulfamethoxazole (22.7%) among ESBL producers highlights its role in settings with high resistance to conventional agents [19]. However, the 21.4% resistance rate, particularly in *K. pneumoniae*, raises concerns about its long-term sustainability. Combination therapies or susceptibility-guided prescribing may mitigate resistance emergence, as suggested by ongoing trials [20]. Local susceptibility data, as provided here, are critical for tailoring empirical therapy, especially in regions with high ESBL prevalence, and support fosfomycin's inclusion in UTI treatment guidelines pending further clinical outcome studies.

CONCLUSIONS

This study demonstrates that fosfomycin retains substantial in vitro activity against ESBL-producing gram-negative bacilli causing UTIs, with 78.6% susceptibility overall and 85.3% for *E. coli*. These findings support its use as an effective oral therapy, particularly for outpatient management of *E. coli*-related infections, reducing reliance on intravenous antibiotics. However, lower susceptibility in *K. pneumoniae* (67.4%) and a 21.4% resistance rate highlight the need for susceptibility testing before prescribing, especially in inpatient settings where resistance is higher. The association between prior antibiotic exposure and resistance underscores the importance of stewardship to preserve fosfomycin's efficacy. Moving forward, integrating fosfomycin into local UTI treatment protocols appears justified, but its use should be guided by microbiological data to optimize outcomes and curb resistance by addressing these gaps, fosfomycin can solidify its role as a cornerstone in the fight against ESBL-related UTIs, offering a practical solution in an era of escalating antibiotic resistance.

CONTRIBUTION OF AUTHORS

One author has only contributed to this article.

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