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Original Research Article

Evaluation of Fosfomycin Susceptibility among Multidrug Resistant Gram Negative Urinary Isolates in a Tertiary Care Hospital

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Abstract

Background: Urinary tract infections (UTIs) caused by multidrug-resistant (MDR) Gram-negative bacteria are increasingly difficult to treat because of the rising prevalence of extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant organisms. Fosfomycin has re-emerged as a promising therapeutic option owing to its unique mechanism of action and preserved activity against resistant uropathogens. This study evaluated the in vitro susceptibility of fosfomycin among MDR Gram-negative urinary isolates.

Materials and Methods: This prospective study was conducted at Rajiv Gandhi Government General Hospital, Chennai, from April to September 2017. A total of 100 MDR Gram-negative urinary isolates, including ESBL-producing and carbapenem-resistant isolates, were studied. Identification was performed using standard microbiological methods. Antimicrobial susceptibility testing was carried out by the Kirby–Bauer disc diffusion method according to CLSI guidelines. Carbapenemase production was detected by the imipenem–EDTA synergy test. Fosfomycin susceptibility was assessed using a 200-µg disc containing glucose-6-phosphate, and minimum inhibitory concentrations (MICs) were determined by E-test.

Results: Escherichia coli was the predominant isolate (36%), followed by Klebsiella pneumoniae (26%), Klebsiella oxytoca (20%), Pseudomonas spp. (12%), and Acinetobacter spp. (6%). Overall fosfomycin susceptibility was 87.0%. Susceptibility was highest in Pseudomonas spp. (100.0%) and E. coli (97.2%), followed by K. pneumoniae (88.5%) and K. oxytoca (80.0%), whereas Acinetobacter spp. showed only 16.7% susceptibility. Fosfomycin susceptibility was 68.4% among ESBL-producing isolates and 91.4% among carbapenem-resistant isolates. Most E. coli and Klebsiella isolates demonstrated low MIC values.

Conclusion: Fosfomycin exhibited excellent in vitro activity against most MDR Gram-negative urinary isolates, particularly carbapenem-resistant E. coli and Klebsiella species, supporting its use as an effective therapeutic option for selected MDR UTIs alongside ongoing antimicrobial surveillance.

Keywords: Urinary tract infection; Fosfomycin; Multidrug-resistant Gram-negative bacteria; ESBL; Carbapenem-resistant Enterobacterales; Antimicrobial susceptibility; Minimum inhibitory concentration.

Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide and represent a major cause of morbidity in both community and hospital settings. Gram-negative bacteria, particularly Escherichia coli and Klebsiella pneumoniae, are the predominant uropathogens, while Pseudomonas aeruginosa and Acinetobacter baumannii are increasingly associated with healthcare-associated UTIs.[1]

The growing burden of antimicrobial resistance among these organisms has significantly complicated UTI management, leading to increased treatment failure, prolonged hospitalization, higher healthcare costs, and poor clinical outcomes.[2]The emergence of multidrug-resistant (MDR) Gram-negative bacteria has become a major global public health concern. MDR organisms are defined as isolates resistant to at least one antimicrobial agent in three or more antibiotic classes.[2]

Resistance develops through several mechanisms, including reduced membrane permeability, activation of efflux pumps, alteration of drug targets, and production of β-lactamases. Among these, extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, and carbapenemases are the most clinically important, as they confer resistance to commonly prescribed β-lactam antibiotics.[1,3] The increasing prevalence of ESBL- and metallo-β-

lactamase (MBL)-producing uropathogens has markedly reduced therapeutic options, particularly in tertiary care hospitals where MDR pathogens are frequently encountered.[4]

The rapid increase in resistance to fluoroquinolones, cephalosporins, aminoglyco sides, and carbapenems has renewed interest in older antimicrobial agents with unique mechanisms of action. Fosfomycin, a phosphonic acid derivative originally isolated from Streptomyces species, has re-emerged as an effective treatment option for UTIs caused by MDR Gram-negative bacteria.[5] It acts by irreversibly inhibiting UDP-N-acetylglu cosamine enolpyruvyl transferase (MurA), thereby blocking the first step of bacterial cell wall synthesis. Because this mechanism is distinct from those of other antimicrobial classes, fosfomycin exhibits minimal cross-resistance and retains activity against many ESBL-producing and selected carbapenem-resistant Gram-negative pathogens.[5]Fosfomycin possesses several pharmacokinetic advantages that make it particularly suitable for treating UTIs. After a single oral 3-g dose of fosfomycin trometamol, high urinary concentrations are rapidly achieved and remain above therapeutic levels for 24–48 hours. Approximately 90–95% of the drug is excreted unchanged in urine, resulting in excellent urinary antibacterial activity.[5]

Clinical studies have demonstrated favorable microbiological eradication and clinical cure rates in uncomplicated cystitis, infections caused by ESBL-producing organisms, asymptomatic bacteriuria during pregnancy, and selected pediatric UTIs. Additionally, fosfomycin has shown synergistic activity with other antimicrobials against biofilm-forming MDR pathogens, expanding its potential role in selected complicated infections.[5] Despite these advantages, fosfomycin susceptibility varies across geographical regions because of differences in antimicrobial prescribing practices and local resistance patterns.[4,6] Moreover, the emergence of resistance during therapy highlights the need for continuous surveillance and judicious antimicrobial use.[7]

Periodic assessment of local susceptibility profiles is therefore essential for guiding empirical therapy, developing institutional antibiotic policies, and strengthening antimicrobial stewardship programs, particularly in tertiary care hospitals where MDR infections are common.[2,4]In view of the increasing prevalence of MDR Gram-negative uropathogens and the limited availability of effective oral treatment options, the present study was undertaken to evaluate the susceptibility of fosfomycin among multidrug-resistant Gram-negative urinary isolates in a tertiary care hospital.

Materials and Methods

This prospective observational study was conducted in the Department of Microbiology at Rajiv Gandhi Government General Hospital, Chennai, over a six-month. The study was undertaken to evaluate the susceptibility of fosfomycin among multidrug-resistant (MDR) Gram-negative urinary isolates obtained from patients with suspected urinary tract infections (UTIs).

Study Population: The study population comprised patients admitted to Rajiv Gandhi Government General Hospital with clinically suspected urinary tract infections. A total of 100 non-duplicate multidrug-resistant Gram-negative urinary isolates were included in the study.

Sample Collection: Urine samples received in the microbiology laboratory from eligible patients were processed according to standard microbiological procedures. Gram-negative bacterial isolates demonstrating carbapenem resistance and/or extended-spectrum β-lactamase (ESBL) production were selected for further evaluation. Only one isolate per patient was included in the analysis.

Inclusion Criteria

- Gram-negative urinary isolates demonstrating resistance to carbapenems.
- Extended-spectrum β-lactamase (ESBL)-producing Gram-negative urinary isolates.

Exclusion Criteria

- Patients younger than 18 years of age.
- Repeated urinary isolates obtained from the same patient.

Isolation and Identification of Bacterial Isolates: Urine specimens were cultured using standard microbiological techniques. Gram-negative bacterial isolates were identified based on colony morphology, Gram staining characteristics, and relevant biochemical tests according to standard laboratory protocols.

Antimicrobial Susceptibility Testing: Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method on Mueller–Hinton agar in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines. The susceptibility profiles of all isolates to routinely tested antimicrobial agents were recorded.

Detection of Carbapenemase Production: Carbapenemase production was detected by the imipenem–EDTA combined disc synergy test for the identification of metallo-β-lactamase (MBL)-producing isolates. Enhancement of the inhibition zone around the imipenem–EDTA disc compared with the imipenem disc alone was interpreted as indicative of MBL production.

Fosfomycin Susceptibility Testing: Fosfomycin susceptibility was determined by the Kirby–Bauer disc diffusion method on Mueller–Hinton agar using fosfomycin discs containing 200 µg of fosfomycin supplemented with 50 µg of glucose-6-phosphate. Zone diameters were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria.

Determination of Minimum Inhibitory Concentration: The minimum inhibitory concentration (MIC) of fosfomycin was determined using fosfomycin E-test strips supplemented with glucose-6-phosphate. The MIC values were read at the point where the elliptical zone of inhibition intersected the scale on the strip and were interpreted according to CLSI and EUCAST recommendations.

Data Analysis: The microbiological findings and antimicrobial susceptibility results were compiled and analyzed using descriptive statistical methods. Categorical variables were expressed as frequencies and percentages to describe the distribution of multidrug-resistant Gram-negative urinary isolates and their susceptibility to fosfomycin.

Results

A total of 100 multidrug-resistant Gram-negative urinary isolates were included in the study. Escherichia coli was the predominant isolate, accounting for 36% of all isolates, followed by Klebsiella pneumoniae (26%), Klebsiella oxytoca (20%), Pseudomonas spp. (12%), and Acinetobacter spp. (6%). Most isolates were recovered from the Medicine Ward (33%), followed by the Surgery Ward (26%), Urology Ward (25%), ICU (10%), and Outpatient Department (6%) (Table 1).

Among the 100 MDR isolates, 19 were ESBL producers and 81 were carbapenem-resistant isolates. Fosfomycin susceptibility among ESBL-producing isolates was highest in Pseudomonas spp. (100%), followed by Escherichia coli (88.9%), Klebsiella oxytoca (66.7%), and Klebsiella pneumoniae (50.0%), while none of the Acinetobacter spp. isolates were susceptible. Among carbapenem-resistant isolates, fosfomycin demonstrated excellent activity against Escherichia coli and Pseudomonas spp. (100% each), followed by Klebsiella pneumoniae (91.7%) and Klebsiella oxytoca (82.4%), whereas susceptibility among Acinetobacter spp. was only 33.3%. Overall, fosfomycin susceptibility was observed in 68.4% of ESBL-producing isolates and 91.4% of carbapenem-resistant isolates (Table 2, Figure 1).

Minimum inhibitory concentration (MIC) testing demonstrated low fosfomycin MIC values for the majority of isolates. Thirty-five of 36 Escherichia coli isolates had an MIC of 1 µg/mL, while one isolate had an MIC of 2 µg/mL. Most Klebsiella oxytoca (80%) and Klebsiella pneumoniae (88.5%) isolates demonstrated an MIC of 2 µg/mL, whereas all Pseudomonas spp. isolates exhibited an MIC of <0.5 µg/mL. In contrast, Acinetobacter spp. showed comparatively higher MIC values, with five of six isolates exhibiting an MIC of 16 µg/mL (Table 3). Overall, fosfomycin demonstrated high in vitro activity against multidrug-resistant Gram-negative urinary isolates, with an overall susceptibility rate of 87.0%. Susceptibility was highest among Pseudomonas spp. (100.0%) and Escherichia coli (97.2%), followed by Klebsiella pneumoniae (88.5%) and Klebsiella oxytoca (80.0%). Acinetobacter spp. exhibited the lowest susceptibility rate (16.7%) (Table 4, Figure 2).

Table 1: Distribution of multidrug-resistant Gram-negative uropathogens according to hospital location (n = 100)

Gram-negative bacteria	OP	Medicine ward	Urology ward	ICU	Surgery ward	Total, n (%)
Escherichia coli	3	8	9	2	14	36 (36.0)
Klebsiella pneumoniae	0	12	6	3	5	26 (26.0)
Klebsiella oxytoca	1	9	5	3	2	20 (20.0)
Pseudomonas spp.	2	3	2	1	4	12 (12.0)
Acinetobacter spp.	0	1	3	1	1	6 (6.0)
Total	**6**	**33**	**25**	**10**	**26**	**100 (100.0)**

Table 2: Distribution of ESBL-producing and carbapenem-resistant Gram-negative urinary isolates with fosfomycin susceptibility (n = 100)

Organism	ESBL producers n	Fosfomycin susceptible n (%)	Carbapenem-resistant isolates n	Fosfomycin susceptible n (%)
Escherichia coli	9	8 (88.9)	27	27 (100.0)
Klebsiella oxytoca	3	2 (66.7)	17	14 (82.4)
Klebsiella pneumoniae	2	1 (50.0)	24	22 (91.7)
Pseudomonas spp.	2	2 (100.0)	10	10 (100.0)
Acinetobacter spp.	3	0 (0.0)	3	1 (33.3)
Total	**19**	**13 (68.4)**	**81**	**74 (91.4)**

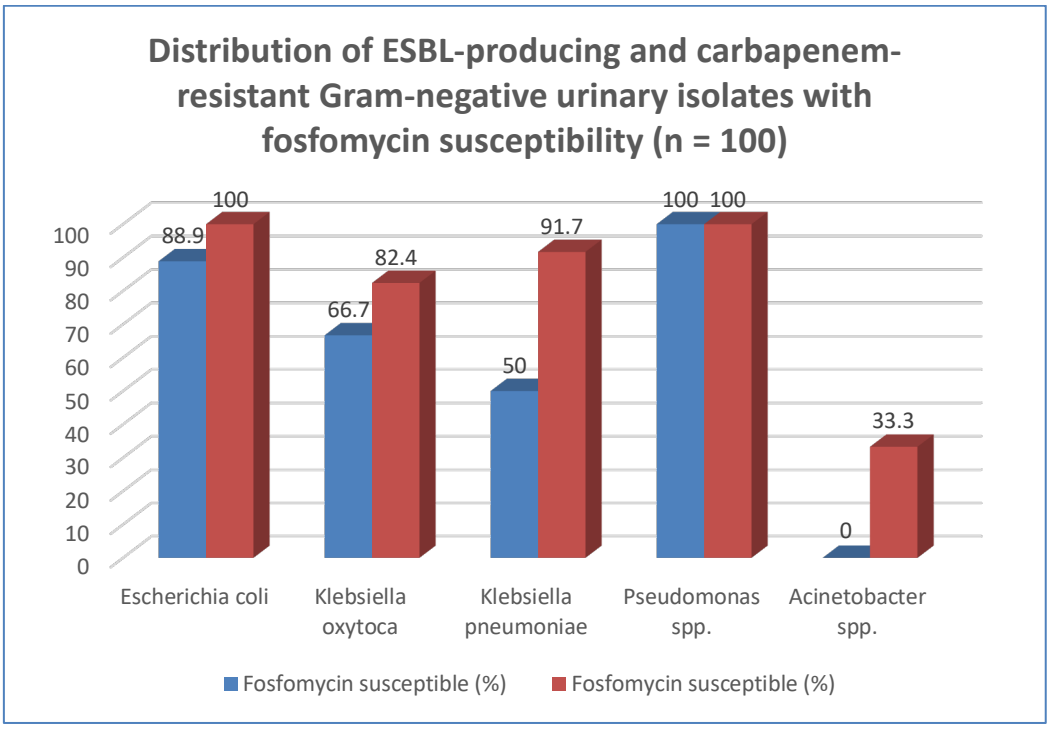

Figure 1: Distribution of ESBL-producing and carbapenem-resistant Gram-negative urinary isolates with fosfomycin susceptibility (n = 100)

Table 3: Distribution of fosfomycin minimum inhibitory concentration (MIC) among multidrug-resistant Gram-negative urinary isolates (n = 100)

Organism	<0.5	1	2	4	8	16	32	64	128	256
Escherichia coli (n=36)	0	35	1	0	0	0	0	0	0	0
Klebsiella oxytoca (n=20)	0	0	16	0	4	0	0	0	0	0
Klebsiella pneumoniae (n=26)	0	0	23	0	0	3	0	0	0	0
Pseudomonas spp. (n=12)	12	0	0	0	0	0	0	0	0	0
Acinetobacter spp. (n=6)	0	0	0	0	1	5	0	0	0	0

Table 4: Overall fosfomycin susceptibility among multidrug-resistant Gram-negative urinary isolates

Organism	Total isolates	Fosfomycin susceptible	Susceptibility (%)
Escherichia coli	36	35	97.2
Klebsiella pneumoniae	26	23	88.5
Klebsiella oxytoca	20	16	80.0
Pseudomonas spp.	12	12	100.0
Acinetobacter spp.	6	1	16.7
Total	**100**	**87**	**87.0**

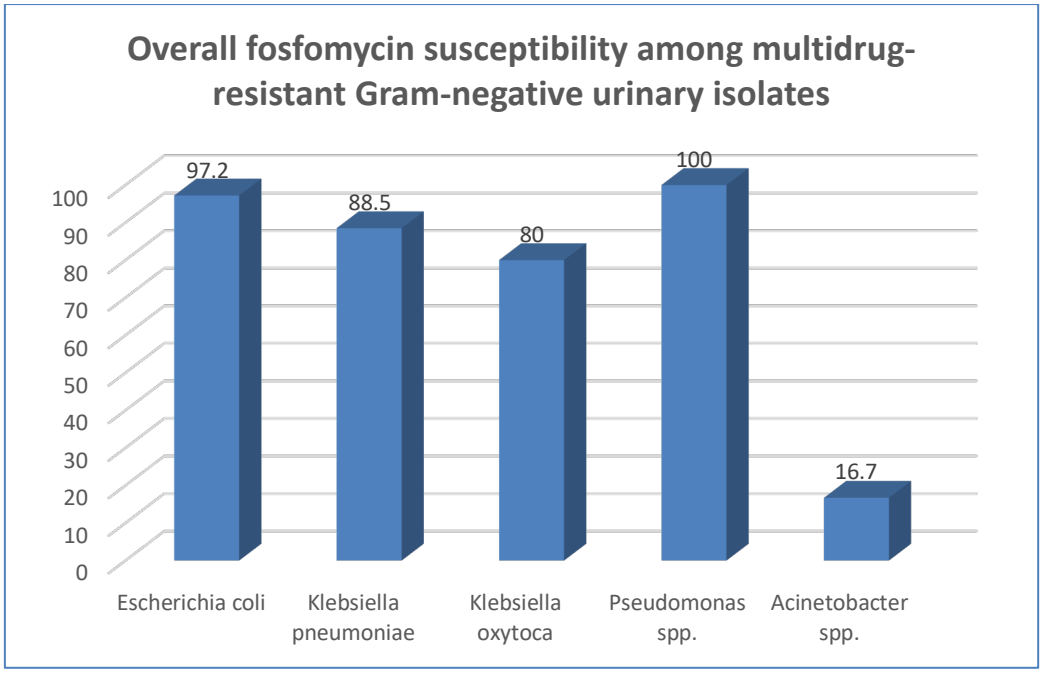

Figure 2: Overall fosfomycin susceptibility among multidrug-resistant Gram-negative urinary isolates

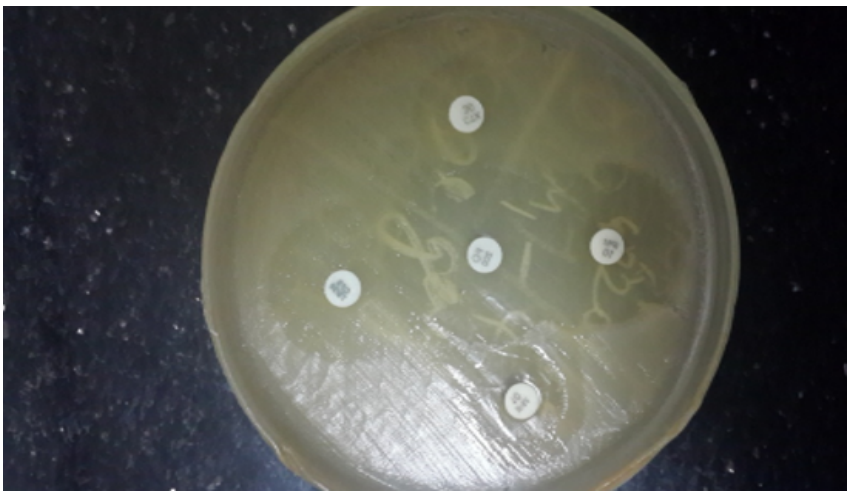

Figure 3: Fosfomycin 200ug disc sensitivity in ESBLs producer &Carbapenem resistant strain

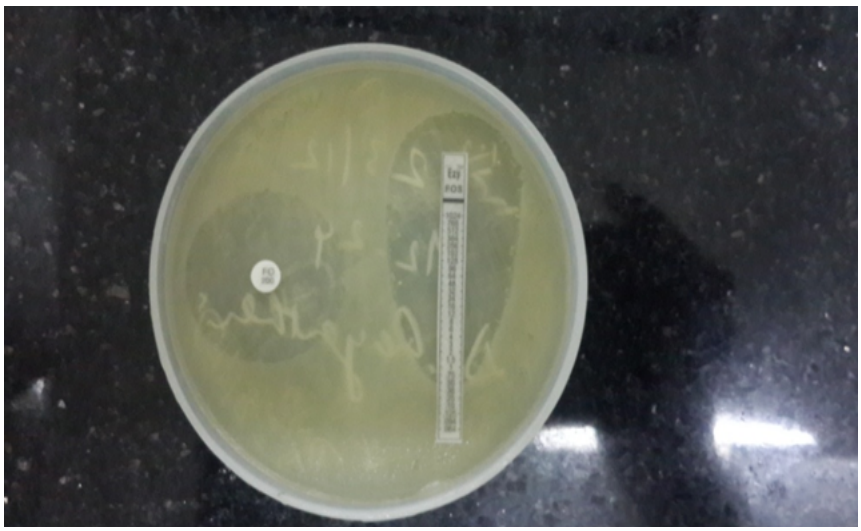

Figure 4: Fosfomycin Sensitivity by disc diffusion method & MIC Determination by E-Strip

Discussion

The increasing prevalence of multidrug-resistant (MDR) Gram-negative uropathogens, particularly extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant isolates, has renewed interest in fosfomycin as an effective therapeutic option for complicated urinary tract infections (UTIs). In the present study, fosfomycin demonstrated an overall susceptibility of 87.0% among MDR urinary isolates, indicating excellent in vitro activity against most resistant uropathogens. Escherichia coli was the predominant isolate (36%), followed by Klebsiella pneumoniae (26%), Klebsiella oxytoca (20%), Pseudomonas spp. (12%), and Acinetobacter spp. (6%). Most isolates originated from the medicine (33%) and surgery (26%) wards, reflecting the burden of healthcare-associated UTIs. Similar organism distributions have been reported by Kaur et al.[8] and Deopa et al.[9], both of whom identified E. coli as the leading uropathogen despite increasing antimicrobial resistance.

A major finding of the present study was the excellent activity of fosfomycin against E. coli, with an overall susceptibility of 97.2%, including 100% susceptibility among carbapenem-resistant isolates and 88.9% among ESBL producers. Comparable results have been reported by Amladi et al.[10], who observed 98.9% susceptibility among carbapenem-resistant E. coli, and Behera et al.[11], who demonstrated 99% susceptibility among urinary E. coli isolates. Kaur et al.[8] likewise reported susceptibility exceeding 94%, supporting fosfomycin as an effective carbapenem-sparing agent against MDR E. coli. Overall susceptibility among Klebsiella pneumoniae was 88.5%, with 91.7% susceptibility among carbapenem-resistant isolates but only 50% among ESBL producers, suggesting emerging resistance in this subgroup. Similar high susceptibility among carbapenem-resistant Klebsiella has been reported by Amladi et al.[10] and Behera et al.[11]. Klebsiella oxytoca showed an overall susceptibility of 80%, including 82.4% among carbapenem-resistant isolates and 66.7% among ESBL producers, consistent with previous reports indicating slightly lower susceptibility in Klebsiella species than in E. coli because of intrinsic fosA-mediated resistance mechanisms. All Pseudomonas isolates were susceptible to fosfomycin (100%), suggesting potential utility against selected MDR urinary infections. However, Behera et al.[11] reported only 66% susceptibility, emphasizing regional variation in resistance patterns. In contrast, Acinetobacter spp. demonstrated poor susceptibility (16.7% overall), with only 33.3% susceptibility among carbapenem-resistant isolates and no susceptible ESBL-producing isolates. Similar findings have been documented by Behera et al.[11] and Kaur et al.[8], indicating limited clinical utility of fosfomycin against MDR Acinetobacter. Among the 19 ESBL-producing and 81 carbapenem-resistant isolates, overall susceptibility was 68.4% and 91.4%, respectively. These findings agree with Amladi et al.[10], who demonstrated excellent activity against carbapenem-resistant Enterobacterales, and Patel et al.[12], who also reported high fosfomycin susceptibility among resistant Enterobacteriaceae. MIC analysis further supported these results, with low MICs for E. coli and Klebsiella isolates, comparable to observations by Amladi et al.[10].

Conclusion

Fosfomycin demonstrated excellent in vitro activity against multidrug-resistant Gram-negative urinary isolates, with an overall susceptibility of 87.0%. The highest susceptibility was observed among Escherichia coli and Pseudomonas spp., while good activity was also noted against carbapenem-resistant Klebsiella species. In contrast, limited activity was observed against Acinetobacter spp. These findings support the use of fosfomycin as an effective therapeutic option for selected multidrug-resistant urinary tract infections and emphasize the importance of continued antimicrobial surveillance and stewardship to preserve its clinical efficacy.

Limitations

The study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings. Clinical outcomes of patients treated with fosfomycin were not evaluated, as the study assessed only in vitro susceptibility. Molecular characterization of resistance mechanisms, including fosfomycin resistance genes, was not performed, which could have provided additional insight into resistance patterns.

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