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FOSFOMYCIN RESISTANCE AMONG UROPATHOGENIC *ESCHERICHIA COLI* ISOLATES WITH EMPHASIS ON ESBL PRODUCTION: A TERTIARY CARE HOSPITAL – BASED STUDY

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ABSTRACT

Background: Fosfomycin is an important oral option for urinary tract infection (UTI) caused by multidrug-resistant (MDR) Enterobacterales, but resistance is emerging and data on its relationship with different β-lactamase phenotypes are limited from India. The present study aimed to determine the prevalence of fosfomycin resistance among clinical isolates of *E.coli.*

Methods: In this cross-sectional study, 383 urinary isolates of *Escherichia coli* from patients with clinically diagnosed UTI were tested for antimicrobial susceptibility by Kirby–Bauer disk diffusion (CLSI M100, 34th edition). ESBL, AmpC and carbapenemase production were detected phenotypically (double-disk diffusion, combination-disk and modified carbapenem inactivation methods, respectively); bla_{TEM} and $bla_{\text{CTX-M}}$ were detected by PCR in 190 isolates. Fosfomycin MIC was determined by agar dilution. Groups were compared using chi-square, Fisher's exact and Welch t-tests.

Results: The mean patient age was 38 ± 16 years; 56.4% were female and 85.9% were in-patients. ESBL, AmpC and carbapenemase production were found in 49.1% (188/383), 33.7% (129/383) and 11.2% (43/383) of isolates, and 63.7% (244/383) were MDR. Among PCR-tested isolates, $bla_{\text{CTX-M}}$ and bla_{TEM} were present in 96.8% and 92.1%. Fosfomycin had the lowest resistance of all agents (2.3%, 9/383; 95% CI 1.2–4.4), with MIC_{50}/MIC_{90} of 0.5/1.0 µg/mL. All nine resistant isolates were ESBL-positive and MDR. Fosfomycin resistance was significantly more frequent in ESBL-positive (4.8% vs 0%; p = 0.0015), AmpC-positive (5.4% vs 0.8%; p = 0.0081) and MDR isolates (3.7% vs 0%; p = 0.029), but not by carbapenemase status, sex or care setting.

Conclusion: Fosfomycin retained excellent in vitro activity (≥94.6% susceptibility) against ESBL-, AmpC- and MDR *E. coli*, although the few resistant isolates were confined to ESBL-producing MDR strains. Continued susceptibility surveillance is warranted to preserve this agent.

KEYWORDS: Fosfomycin, *Escherichia coli*, extended-spectrum β-lactamase, AmpC, urinary tract infection, antimicrobial resistance

INTRODUCTION

Urinary tract infection (UTI) is among the commonest bacterial infections in community and hospital settings and causes considerable morbidity [1,2]. *Escherichia coli* accounts for 70–90% of cases, followed by *Klebsiella pneumoniae*, *Proteus mirabilis*, non-fermenting Gram-negative bacilli and enterococci [1,2].

The global rise of multidrug resistance among uropathogens is of grave concern. Extended-spectrum β-lactamase (ESBL)-producing Enterobacterales are the most troublesome, because they are frequently co-resistant to fluoroquinolones, aminoglycosides and cotrimoxazole, which markedly limits oral treatment options [3,4]. Production of AmpC β-lactamases and carbapenemases further narrows therapy, and early detection of such isolates is essential for effective treatment.

Fosfomycin is a broad-spectrum bactericidal phosphonic acid derivative that inhibits UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), the first committed step in peptidoglycan synthesis [5]. It is recommended as a first-line agent for uncomplicated cystitis [6], and a systematic review found that 96.8% of ESBL-producing Enterobacteriaceae isolates were susceptible [7]. Because of these properties, the drug has re-emerged as an attractive oral alternative against MDR uropathogens [8].

Increasing use, however, raises concern about the emergence of resistance [9]. Reported fosfomycin resistance among urinary *E. coli* varies widely, from 2.2% in community isolates from South Africa [10] and 6.1% in MDR uropathogens [11] to 24.1% in Egypt [12] and 37.5% among children [13]. Resistance is consistently higher among

ESBL producers; in Madrid it was 14.3% in 2013 and about 20% in 2018–2021 [14]. Plasmid-mediated *fosA3* has been implicated in resistant isolates [15,16]. Data from India remain limited [17,18], and few studies have examined fosfomycin resistance across ESBL, AmpC and carbapenemase phenotypes together in the same isolate collection.
The present study therefore aimed to determine the prevalence of fosfomycin resistance among clinical *E.coli* isolates and assess its association with resistance mechanisms, multidrug resistance and patient characteristics.

MATERIALS AND METHODS

Study design, setting and reporting

This cross-sectional study was conducted in the Department of Microbiology, Santosh Medical College and Hospital, Ghaziabad, in collaboration with the Department of Microbiology, Al-Falah School of Medical Science and Research Centre, Faridabad, India. The study is reported in accordance with the STROBE statement [19]. The protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants.

Sample size and study population

The sample size was calculated using $n = Z^2_{1-\alpha/2} \cdot P(1-P)/d^2$, with an expected proportion (P) of 51.64% from a previous Indian study [20], 95% confidence and 5% absolute precision, giving 383 isolates. Patients with clinically diagnosed UTI of either sex, whose samples were collected, received and processed in time. Patients receiving antibiotic therapy or immunosuppressive drugs, samples yielding more than three bacterial types or contaminated growth, and leaking or open containers were excluded.

Isolation and identification

Urine was collected aseptically in sterile leak-proof containers and examined microscopically (wet mount and Gram stain) for pus cells and bacteria. Samples were inoculated onto cystine lactose electrolyte-deficient (CLED) agar and incubated overnight at 37 °C. Plates showing significant growth of a single organism were processed further; samples with insignificant or polymicrobial growth were discarded and repeat collection was requested. Isolates were identified by colony morphology, Gram staining and standard biochemical tests.

Antimicrobial susceptibility testing

Susceptibility to 21 antimicrobial agents (cephalosporins, cefoxitin, aztreonam, penicillin–β-lactamase inhibitor combinations, fluoroquinolones, tetracycline, cotrimoxazole, aminoglycosides, nitrofurantoin, carbapenems and fosfomycin) was tested by the Kirby–Bauer disk diffusion method on Mueller–Hinton agar and interpreted according to CLSI M100, 34th edition [21]. Fosfomycin was tested using fosfomycin 200 µg disks containing 50 µg glucose-6-phosphate. *E. coli* ATCC 25922 was used for quality control. Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories [23].

Detection of ESBL, AmpC and carbapenemase production

Isolates were screened for ESBL, AmpC and carbapenemase production. ESBL production was confirmed by the double-disk diffusion test, AmpC production by a combination-disk diffusion test, and carbapenemase production by the modified carbapenem inactivation method (mCIM) [22]. The presence of bla_{TEM} and $bla_{\text{CTX-M}}$ was determined by polymerase chain reaction (PCR) in 190 isolates.

Fosfomycin minimum inhibitory concentration

The MIC of fosfomycin was determined by the agar dilution method for all 383 isolates, and MIC_{50}, MIC_{90} and geometric mean MIC were derived.

Statistical analysis

Data were compiled in Microsoft Excel and analysed in SPSS Trial version. Age was summarised as mean ± standard deviation (SD) and median (range); categorical variables as frequencies and percentages. Ninety-five percent confidence intervals for proportions were calculated by the Wilson score method. Resistance was compared between ESBL-positive and -negative, AmpC-positive and -negative, male and female, and in-patient (IPD) and out-patient (OPD) groups using the chi-square test, or Fisher's exact test when any expected cell count was below five. Age was compared using Welch's independent-samples t-test. A two-tailed p-value <0.05 was considered significant; no adjustment was made for multiple comparisons.

RESULTS

Study population

A total of 383 *E. coli* isolates, one from each patient, were analysed. The mean age was 38 ± 16 years (median 34.5; range 2–84), and most patients (57.9%) were aged 20–39 years. Females constituted 56.4% of patients, and 85.9% were in-patients, mainly from obstetrics and gynaecology (28.6%) and general medicine (26.6%) (Table 1). Urgency and frequency was the commonest presentation (68.9%), and cystitis the commonest clinical diagnosis (66.8%).

Table 1. Demographic and clinical characteristics of the patients (N = 383)

Characteristic	Value
Age, years, mean ± SD	38 ± 16
Age, years, median (range)	34.5 (2–84)

Characteristic	Value
Age group, n (%)	
<20 years	17 (4.5)
20–39 years	221 (57.9)
40–59 years	91 (23.8)
≥60 years	53 (13.9)
Sex, n (%)	
Female	216 (56.4)
Male	167 (43.6)
Care setting, n (%)	
In-patient (IPD)	329 (85.9)
Out-patient (OPD)	54 (14.1)
Ward, n (%)	
Obstetrics and gynaecology	109 (28.6)
General medicine	102 (26.6)
Surgery	58 (15.2)
OPD	54 (14.1)
Intensive care units (MICU, ICCU)	51 (13.3)
Other	9 (2.3)
Presenting symptoms, n (%)	
Urgency, frequency	264 (68.9)
Fever with vomiting	81 (21.1)
Fever alone	22 (5.7)
Other	16 (4.2)
Clinical diagnosis, n (%)	
Cystitis	256 (66.8)
Dysuria, urgency	93 (24.3)
Bacteriuria	13 (3.4)
Other	21 (5.5)

SD, standard deviation; MICU, medical intensive care unit; ICCU, intensive cardiac care unit.

Antimicrobial susceptibility

Resistance was highest to third-generation cephalosporins (ceftriaxone 71.8%, cefotaxime 70.0%) and lowest to fosfomycin (2.3%), followed by tobramycin (5.7%), amikacin (8.4%) and nitrofurantoin (9.1%) (Figure 1). Resistance to fluoroquinolones ranged from 43.3% to 46.5%, to tetracycline was 44.1%, to piperacillin–tazobactam 27.2%, and to imipenem and meropenem 11.2% each.

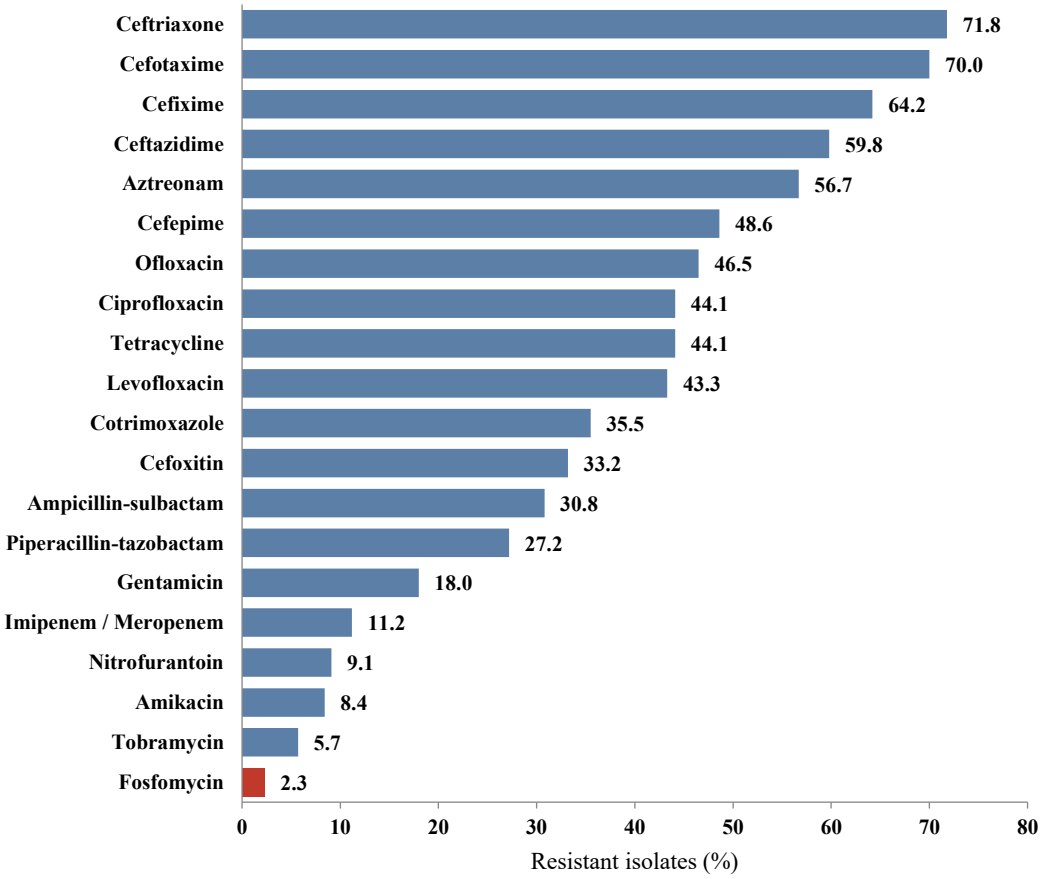


Figure 1. Resistance rates (%) of 383 urinary *E. coli* isolates to antimicrobial agents

Resistance mechanisms and multidrug resistance

ESBL production was detected in 49.1% of isolates, AmpC in 33.7% and carbapenemase (mCIM) in 11.2%; 63.7% were MDR (Table 2). Among 190 PCR-tested isolates, $bla_{\text{CTX-M}}$ was detected in 96.8% and bla_{TEM} in 92.1%; 169 isolates (88.9%) carried both genes, 15 carried $bla_{\text{CTX-M}}$ alone, 6 carried bla_{TEM} alone and none was negative for both (Fisher's exact test for association, $p = 1.0$). MDR was significantly commoner in ESBL-positive than in ESBL-negative isolates (93.6% vs 34.9%; $p < 0.001$). ESBL-positive and -negative groups did not differ in age (37.2 ± 16.1 vs 38.7 ± 15.9 years; $p = 0.364$), sex ($p = 0.761$) or care setting ($p = 0.558$). Resistance to none of the antibiotics differed significantly between male and female patients or between IPD and OPD patients (all $p > 0.05$).

Table 2. Prevalence of resistance mechanisms, multidrug resistance and fosfomycin resistance

Characteristic	n/N	%	95% CI
ESBL production	188/383	49.1	44.1–54.1
AmpC production	129/383	33.7	29.1–38.6
Carbapenemase production (mCIM)	43/383	11.2	8.4–14.8
Multidrug resistance (MDR)	244/383	63.7	58.8–68.4
Fosfomycin resistance	9/383	2.3	1.2–4.4
PCR-tested subset (n = 190)			
$bla_{\text{CTX-M}}$ present	184/190	96.8	93.3–98.5
bla_{TEM} present	175/190	92.1	87.4–95.2
Both genes present	169/190	88.9	83.7–92.7

ESBL, extended-spectrum β-lactamase; mCIM, modified carbapenem inactivation method; CI, Wilson 95% confidence interval.

Resistance in relation to ESBL and AmpC production

Resistance was significantly higher in ESBL-positive than ESBL-negative isolates for all 21 agents tested (all $p < 0.05$), and in AmpC-positive than AmpC-negative isolates for 20 of 21 agents; the exception was amikacin (12.4%

vs 6.3%; p = 0.065) (Table 3). Carbapenem resistance was 21.8% in ESBL producers versus 1.0% in non-producers, and 29.5% in AmpC producers versus 2.0% in non-producers (p <0.001).

Table 3. Resistance to selected antibiotics by ESBL and AmpC status, n (%)

Antibiotic	ESBL+ (n=188)	ESBL− (n=195)	p	AmpC+ (n=129)	AmpC− (n=254)	p
Ceftriaxone	184 (97.9)	91 (46.7)	<0.001	129 (100)	146 (57.5)	<0.001
Cefepime	172 (91.5)	14 (7.2)	<0.001	118 (91.5)	68 (26.8)	<0.001
Piperacillin–tazobactam	95 (50.5)	9 (4.6)	<0.001	98 (76.0)	6 (2.4)	<0.001
Ciprofloxacin	117 (62.2)	52 (26.7)	<0.001	102 (79.1)	67 (26.4)	<0.001
Gentamicin	51 (27.1)	18 (9.2)	<0.001	34 (26.4)	35 (13.8)	0.004
Amikacin	26 (13.8)	6 (3.1)	<0.001	16 (12.4)	16 (6.3)	0.065
Nitrofurantoin	28 (14.9)	7 (3.6)	<0.001	26 (20.2)	9 (3.5)	<0.001
Imipenem / meropenem	41 (21.8)	2 (1.0)	<0.001	38 (29.5)	5 (2.0)	<0.001
Fosfomycin	9 (4.8)	0 (0.0)	0.0015	7 (5.4)	2 (0.8)	0.008

Chi-square or Fisher's exact test. + , producer; −, non-producer. Full data for all 21 agents are available from the authors.

Fosfomycin susceptibility, MIC and associated factors

Of 383 isolates, 374 (97.7%; 95% CI 95.6–98.8) were categorised as fosfomycin-susceptible and nine (2.3%; 95% CI 1.2–4.4) as resistant. Fosfomycin MICs were 0.5 µg/mL in 315 isolates (82.2%) and 1.0 µg/mL in 68 (17.8%), giving MIC_{50} 0.5 µg/mL, MIC_{90} 1.0 µg/mL and a geometric mean MIC of 0.57 µg/mL; no isolate exceeded 1.0 µg/mL. Susceptibility remained high among ESBL-positive (95.2%, 179/188), AmpC-positive (94.6%, 122/129), mCIM-positive (95.3%, 41/43) and MDR isolates (96.3%, 235/244).

All nine fosfomycin-resistant isolates were ESBL-positive and MDR, seven were AmpC-positive and two were mCIM-positive. Fosfomycin resistance was significantly associated with ESBL production, AmpC production and MDR status, but not with mCIM status, sex or care setting (Table 4, Figure 2). An MIC of 1.0 µg/mL was significantly more frequent in ESBL-positive isolates (22.3% vs 13.3%; p = 0.030) but did not differ by any other factor. The proportion with an MIC of 1.0 µg/mL was similar in resistant (1/9) and susceptible isolates (67/374; p = 1.000).

Table 4. Fosfomycin resistance and higher MIC (1.0 µg/mL) in relation to resistance mechanisms and patient factors

Comparison (first vs second group)	Resistant, first group n/N (%)	Resistant, second group n/N (%)	p	MIC 1.0, first group n/N (%)	MIC 1.0, second group n/N (%)	p
ESBL positive vs negative	9/188 (4.8)	0/195 (0.0)	0.0015	42/188 (22.3)	26/195 (13.3)	0.030
AmpC positive vs negative	7/129 (5.4)	2/254 (0.8)	0.008	25/129 (19.4)	43/254 (16.9)	0.652
mCIM positive vs negative	2/43 (4.7)	7/340 (2.1)	0.267	8/43 (18.6)	60/340 (17.6)	1.000
MDR vs non-MDR	9/244 (3.7)	0/139 (0.0)	0.029	48/244 (19.7)	20/139 (14.4)	0.245
Male vs female	4/167 (2.4)	5/216 (2.3)	1.000	32/167 (19.2)	36/216 (16.7)	0.618
IPD vs OPD	8/329 (2.4)	1/54 (1.9)	1.000	58/329 (17.6)	10/54 (18.5)	1.000

Resistance compared by Fisher's exact test; MIC 1.0 µg/mL compared by chi-square test. IPD, in-patient department; OPD, out-patient department. With only nine resistant isolates, statistical power is limited.

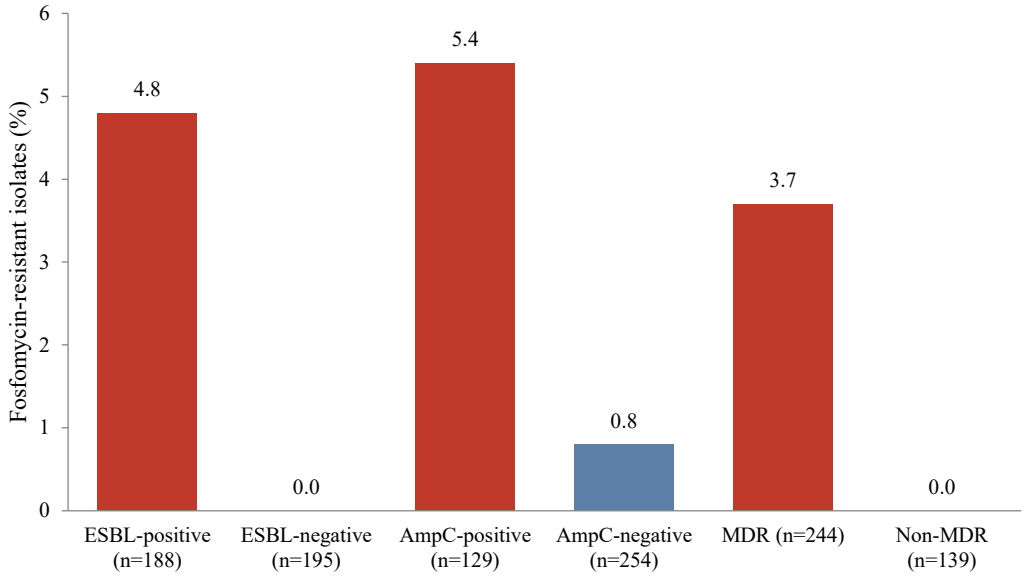


Figure 2. Fosfomycin resistance (%) according to ESBL, AmpC and multidrug-resistance (MDR) status. Fisher's exact test: ESBL p = 0.0015; AmpC p = 0.0081; MDR p = 0.029. The chart is editable (right-click, Edit Data).

DISCUSSION

In this study of 383 urinary *E. coli* isolates, of which nearly half produced ESBL and almost two-thirds were MDR, fosfomycin showed the lowest resistance (2.3%) of all 21 agents tested. Susceptibility remained at or above 94.6% among ESBL-, AmpC- and MDR isolates, consistent with the 96.8% susceptibility reported among ESBL producers in a systematic review [7]. Our resistance rate is close to the 2.2% and 6.1% reported from South Africa [10] and from MDR uropathogens [11], but well below the 24.1% and 37.5% reported from Egypt [12,13], the 25% found in MDR *Enterobacter* species from Bangladesh [24] and the roughly 20% found among ESBL producers in Spain [14]. Such differences probably reflect variation in patient populations, prior antibiotic exposure, the local prevalence of plasmid-borne resistance determinants and, importantly, the testing method used.

The principal finding is that fosfomycin resistance was not evenly distributed: all nine resistant isolates were ESBL-positive and MDR, and resistance was significantly commoner in ESBL-, AmpC- and MDR isolates. This agrees with Ríos et al., who reported a significant association between fosfomycin resistance and ESBL production [14], and with earlier descriptions of fosfomycin resistance acquired by CTX-M-15-producing *E. coli* [25]. Plasmid-mediated *fosA3*, frequently reported alongside $bla_{\text{CTX-M}}$ in resistant *E. coli* [15,16], is a plausible mechanism, and co-selection under antibiotic pressure in hospitalised patients may contribute; however, we did not test for *fos* genes and this remains speculative. The absence of an association with carbapenemase production, sex and care setting should be interpreted cautiously because of the small number of resistant isolates. A modest upward shift in MIC (1.0 µg/mL) in ESBL producers, despite all MICs remaining within a narrow range, supports the same trend.

The burden of β-lactamase production was high. ESBL production (49.1%) and carbapenemase production by mCIM (11.2%) exceed what is desirable for a community-associated infection such as cystitis, probably because most isolates came from hospitalised patients. Among the PCR-tested isolates, $bla_{\text{CTX-M}}$ (96.8%) and bla_{TEM} (92.1%) predominated, and co-carriage of both genes was common (88.9%), in keeping with the worldwide dominance of CTX-M enzymes [26]. The comparison of antibiotic resistance between ESBL- or AmpC-positive and -negative isolates showed markedly higher resistance in producers for almost every agent, including non-β-lactams, which reflects the co-resistance typical of MDR plasmids. Differences for cephalosporins, aztreonam and cefoxitin are partly definitional, because ESBL and AmpC screening relies on these agents, and should not be over-interpreted. Resistance did not differ by sex or between in-patients and out-patients, suggesting that MDR *E. coli* circulates in both settings in this region.

An important point concerns testing methodology. Fosfomycin categorisation is method-dependent, and disk diffusion, agar dilution and other techniques may give discordant results [27]. In our data, the nine isolates categorised as resistant had MICs of only 0.5–1.0 µg/mL, far below the CLSI agar-dilution susceptibility breakpoint for *E. coli* [21].

From a clinical standpoint, the findings support fosfomycin as a useful oral option for uncomplicated cystitis caused by ESBL-, AmpC- and MDR-*E. coli* where fluoroquinolone and cephalosporin resistance is common, in line with reports of its efficacy against MDR isolates [28]. Because susceptibility was high but not universal, and resistance clustered in ESBL-producing MDR strains, fosfomycin should be used judiciously within antimicrobial stewardship programmes, with local surveillance.

Limitations

This study has limitations. Only *E. coli* was analysed, so findings cannot be extended to other uropathogens. Resistance genes were sought by PCR only for bla_{TEM} and $bla_{\text{CTX-M}}$ in a subset of isolates; carbapenemase types and fosfomycin resistance determinants (*fosA*, *murA*, *glpT*, *uhpT*) were not characterised. The small number of resistant

isolates (n = 9) limited statistical power, no correction was made for multiple comparisons, and the ESBL/AmpC comparisons for β-lactams are partly circular. The categorical fosfomycin result and MIC values were discordant, as discussed above. Clinical outcomes and prior antibiotic exposure were not evaluated and hospital-based sampling limits generalizability.

CONCLUSION

Fosfomycin remained highly active in vitro against urinary *E. coli*, including ESBL-, AmpC- and MDR isolates (≥94.6% susceptible) and with the lowest resistance (2.3%) among all agents tested. The few resistant isolates were confined to ESBL-producing MDR strains, and resistance was significantly associated with ESBL, AmpC and MDR phenotypes but not with carbapenemase production. Confirmation by a reference MIC method, molecular characterisation of resistance determinants and continued surveillance are recommended to preserve the utility of this agent.

REFERENCES

1. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28(1):1-13.
2. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269-84.
3. Pitout JDD, Laupland KB. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis. 2008;8(3):159-66.
4. Bush K, Jacoby GA. Updated functional classification of β-lactamases. Antimicrob Agents Chemother. 2010;54(3):969-76.
5. Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. Clin Microbiol Rev. 2016;29(2):321-47.
6. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-20.
7. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis. 2010;10(1):43-50.
8. Sastry S, Doi Y. Fosfomycin: resurgence of an old companion. J Infect Chemother. 2016;22(5):273-80.
9. Karageorgopoulos DE, Wang R, Yu XH, Falagas ME. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012;67(2):255-68.
10. Mosime LB, Newton-Foot M, Nel P. Fosfomycin resistance in community-acquired urinary pathogens from Western Cape, South Africa. South Afr J Infect Dis. 2022;37(1):321.
11. Bir R, Mohapatra S, Kumar A, Arif N, Tyagi S, Ak AP, et al. Genomic analysis of fosfomycin resistance in multi-drug resistant uropathogens and comparison of in-vitro susceptibility methods. Iran J Microbiol. 2022;14(5):636.
12. Mohamed Abu El-Wafa W, Abouwarda AM. In vitro assessment of the antibacterial effects of the combinations of fosfomycin, colistin, trimethoprim and nitrofurantoin against multi-drug-resistant Escherichia coli. Lett Appl Microbiol. 2022;74(3):334-43.
13. Abdelraheem WM, Mahdi WK, Abuelela IS, Hassuna NA. High incidence of fosfomycin-resistant uropathogenic E. coli among children. BMC Infect Dis. 2023;23(1):475.
14. Ríos E, López Díaz MDC, Culebras E, Rodríguez-Avial I, Rodríguez-Avial C. Resistance to fosfomycin is increasing and is significantly associated with extended-spectrum β-lactamase-production in urinary isolates of Escherichia coli. Med Microbiol Immunol. 2022;211(5-6):269-72.
15. Loras C, Mendes AC, Peixe L, Novais Â, Alós JI. Escherichia coli resistant to fosfomycin from urinary tract infections: detection of the fosA3 gene in Spain. J Glob Antimicrob Resist. 2020;21:414-6.
16. Li Y, Zheng B, Li Y, Zhu S, Xue F, Liu J. Antimicrobial susceptibility and molecular mechanisms of fosfomycin resistance in clinical Escherichia coli isolates in mainland China. PLoS One. 2015;10(8):e0135269.
17. Gopichand P, Agarwal G, Natarajan M, Mandal J, Deepanjali S, Parameswaran S, et al. In vitro effect of fosfomycin on multi-drug resistant Gram-negative bacteria causing urinary tract infections. Infect Drug Resist. 2019;12:2005-13.
18. Gupta V, Rani H, Singla N, Kaistha N, Chander J. Determination of extended-spectrum β-lactamases and AmpC production in uropathogenic isolates of Escherichia coli and susceptibility to fosfomycin. J Lab Physicians. 2013;5(2):90-3.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
20. Gohel DA, Dhar A, Gupta SD, Patel R, Dinganka RD. Trends of UTI (urinary tract infection) in India. Eur J Pharm Med Res. 2023;10(2).
21. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 34th ed. CLSI supplement M100. Wayne (PA): CLSI; 2024.

22. Pierce VM, Simner PJ, Lonsway DR, Roe-Carpenter DE, Johnson JK, Brasso WB, et al. Modified carbapenem inactivation method for phenotypic detection of carbapenemase production among Enterobacteriaceae. J Clin Microbiol. 2017;55(8):2321-33.
23. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.
24. Munny NN, Shamsuzzaman SM, Hossain T. Emergence of fosfomycin resistance among isolates of multidrug-resistant Enterobacter species at a tertiary care hospital in Dhaka, Bangladesh. Bangladesh Med Res Counc Bull. 2022;48(3):203-10.
25. Oteo J, Orden B, Bautista V, Cuevas O, Arroyo M, Martínez-Ruiz R, et al. CTX-M-15-producing urinary Escherichia coli O25b-ST131-phylogroup B2 has acquired resistance to fosfomycin. J Antimicrob Chemother. 2009;64(4):712-7.
26. Cantón R, Coque TM. The CTX-M β-lactamase pandemic. Curr Opin Microbiol. 2006;9(5):466-75.
27. Perdigão-Neto LV, Oliveira MS, Rizek CF, Carrilho CM, Costa SF, Levin AS. Susceptibility of multiresistant Gram-negative bacteria to fosfomycin and performance of different susceptibility testing methods. Antimicrob Agents Chemother. 2014;58(3):1763-7.
28. Demir T, Buyukguclu T. Fosfomycin: in vitro efficacy against multidrug-resistant isolates beyond urinary isolates. J Glob Antimicrob Resist. 2017;8:164-8.