DOI: 10.7860/NJLM/2021/45342:2456

Original Article

Microbiology Section

Fosfomycin- Is it a Drug of Choice in Multidrug Resistant *Escherichia Coli*?

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ABSTRACT

Introduction: Urinary Tract Infections (UTIs) caused by Multidrug-Resistant (MDR) gram-negative bacteria, specifically *E. coli*, are a growing concern because of limited therapeutic options. Fosfomycin as a novel oral therapeutic option against the MDR uropathogens has been widely discussed recently.

Aim: To know the local antimicrobial susceptibilities and to evaluate the activity of fosfomycin against Extended-Spectrum Beta-Lactamase (ESBL) producing, Carbapenem-Resistant (CR) and MDR *E. coli* isolates in Southern India.

Materials and Methods: A cross-sectional study was conducted in the Department of Microbiology of a tertiary care hospital from January to December 2019. Pathogenic organisms were identified from the urine samples by conventional biochemical tests. Antibiotic sensitivity testing and ESBL production was tested for *E. coli* strains. Minimum Inhibitory Concentration (MIC) was determined by E-test. Data were analysed using Microsoft Excel 2016. Frequencies and percentages were determined for categorical variables.

Results: Out of the 118 positive isolates yielded after the urine culture, 81 (68.6%) were *E. coli*, 12 (10.16%) were *Klebsiella* spp., 7 (5.93%) were *Acinetobacter* spp, 8 (6.77%) were *Pseudomonas* spp., 5 (4.23%) were *Proteus* spp, and 5 (4.23%) were *Citrobacter* spp. Among 81 *E. coli* isolates, 33 (40.74%) were ESBL producers, 26 (32.09%) were CR, and 10 (12.34%) isolates were found to be MDR. However, all the isolates were found to be fosfomycin susceptible both by disc diffusion method and by E-strips.

Conclusion: Fosfomycin might be a promising antibiotic for the treatment of uncomplicated UTIs due to *E. coli*. It has also shown good activity against ESBL-producing, CR, and MDR *E. coli* isolates.

Keywords: Antibiotics, Drug resistance, Urinary tract infection

INTRODUCTION

The UTIs are estimated to affect approximately 10% of women each year [1]. They are classified as "uncomplicated" or "complicated." Uncomplicated UTIs are those that occur in young, healthy, non-pregnant women; whereas complicated UTIs occur in a woman with diabetes or with a structural abnormality of urinary system or hospital acquired infection. The differentiation between complicated and uncomplicated infections is important because it affects both the spectrum of bacteria involved and the duration of antibiotic treatment [2]. In uncomplicated UTIs, the causative bacteria are predictable. In most cases (80 to 90%), *Escherichia coli* will be the pathogenic organism, others being *Staphylococcus saprophyticus*, *Proteus mirabilis*, *Klebsiella* spp., and other *Enterobacteriaceae* spp [3]. These are usually susceptible to most antibiotics. *Pseudomonas aeruginosa*, *Acinetobacter* spp, *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Staphylococcus aureus*, and *Enterococcus* assume a more prominent role in complicated UTIs. These bacteria are more antibiotic resistant. With the inappropriate and inadvertent use of higher antibiotics, resistance to antimicrobials that had been used frequently as therapeutic options for the treatment of *E.coli* related UTIs (penicillins, cephalosporins, and fluoroquinolones), has been increasing [4]. Additionally, bacteria producing ESBL, CR, and the emergence of MDR bacteria further limits the choice of antimicrobials to the treating physicians [5].

Fosfomycin may be an alternative to the currently used treatments of UTIs. It is a well-tolerated bactericidal drug and has a broad spectrum of activity against most of gram-positive and gram-negative bacteria. Fosfomycin has shown synergistic effect with many antibiotics like 3rd generation cephalosporins, aminoglycosides, and carbapenems [6]. Existing literature suggests the use of fosfomycin for the treatment of UTIs due to ESBL-producing, CR, and MDR strains of *E. coli*. However data regarding in vitro susceptibility of fosfomycin against ESBL, CR, and MDR strains of *E. coli* is lacking in the area where the current study was conducted. This study was therefore undertaken to determine in-vitro fosfomycin susceptibility of ESBL-producing, CR, and MDR strains of *E. coli*.

MATERIALS AND METHODS

Sample Collection and Analysis

A cross-sectional study was conducted from January 2019 to December 2019 in the Department of Microbiology, GEMS&H, Srikakulam, Andhra Pradesh, India, after taking approval from Institutional Ethical Committee (Ref:18/IEC/GEM&H/2018). Clinically diagnosed cases of UTI patients were included in the study. Patients who were already on fosfomycin treatment (based on the information provided in the laboratory requisition form) and culture negative samples were excluded from the study. The number of urine samples based on inclusion and exclusion criteria received during the study period was considered. Total 260 freshly voided midstream specimens of urine were processed in the microbiology laboratory. Collected urine samples were cultured immediately (within 30 minutes) and were inoculated onto Blood agar and MacConkey agar media by calibrated loop technique [7]. After overnight incubation, the samples which showed positive growth of organisms were processed. Organisms were identified by their colony morphology, staining characteristics, haemolysis, motility and other relevant biochemical tests as per standard bacteriological methods [8].

Antibiotic Susceptibility Testing

Antibiogram for all the bacterial isolates were performed on Mueller-Hinton agar plates by Kirby-Bauer disc diffusion method and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines M100-S26 version published in 2016 [9]. All the discs were obtained from Hi-Media Laboratories, Mumbai, India. For *E. coli*, the following discs were used: amoxicillin (20 µg), amikacin (30 µg), cefepime (30 µg), cephalexin (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), cefoperazone-sulbactam (75 µg, 1:1), ciprofloxacin (5 µg),

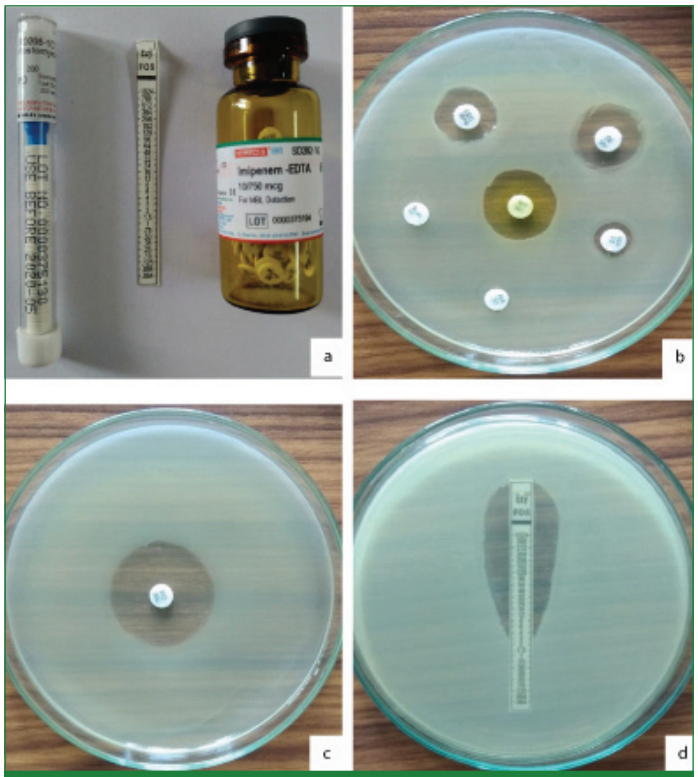
fosfomycin (200 µg), imipenem (10 µg), imipenem-EDTA (10/750 µg), nalidixic acid (30 µg), nitrofurantoin (300 µg), polymixin B (300 µg). *E. coli*: American Type Culture Collection (ATCC) 25922 was used as a control strain.

Detection of ESBLs and Carbapenemases

Cefpodoxime (10 µg), cefotaxime (30 µg), ceftazidime (30 µg) and ceftriaxone (30 µg) discs were used to screen for the ESBL production as per CLSI guidelines. The isolates which tested positive by the screening test were subjected to confirmatory test using ceftazidime (30 µg) and ceftazidime/clavulanic acid (30 µg/10 µg) discs. The results were interpreted according to the CLSI guidelines [9]. Imipenem (10 µg) discs were used to screen for the carbapenemases production. The isolates which tested positive by the screening test were subjected to confirmatory test using Imipenem-EDTA (10/750 µg) discs. The results were interpreted according to the CLSI guidelines [9]. MDR *E. coli* are the isolates that are resistant to at least one agent in three or more classes of antimicrobials [10]. In the present study, it included resistance to any one agent in three of the following groups-cephalosporins, fluoroquinolones, and aminoglycoside.

Fosfomycin Minimum Inhibitory Concentration

MIC of fosfomycin was tested by E-test strip (Hi-Media Laboratories, India) with fosfomycin gradient concentrations ranging from 0.064 µg/mL to 1,024 µg/mL. The E strip was placed at the middle of contact with the agar surface, so that no bubble appeared under the strip and incubation was done at 35°C for 16-18 hours. Interpretation of E-test: <64 µg/mL is sensitive and >64 µg/mL is resistant [Table/Fig-1].



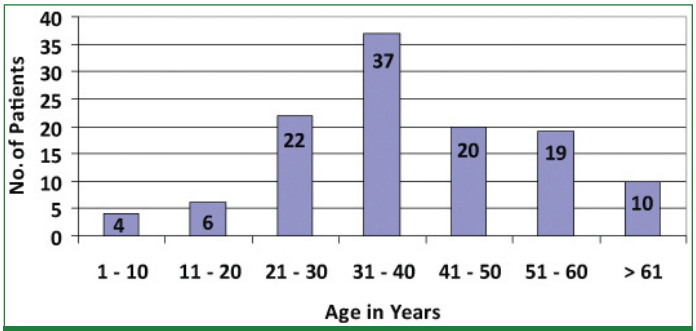
[Table/Fig-1]: Showing a) Fosfomycin disc, fosfomycin E-test Strip, Imipenem-EDTA disc; b) Mueller-Hinton Agar Plate for *E. coli*; c) Fosfomycin sensitive- disk diffusion method; d) Fosfomycin E-test, MIC 3 µg/mL.

STATISTICAL ANALYSIS

Data were analysed using Microsoft Excel 2016. Frequencies and percentages were determined for categorical variables.

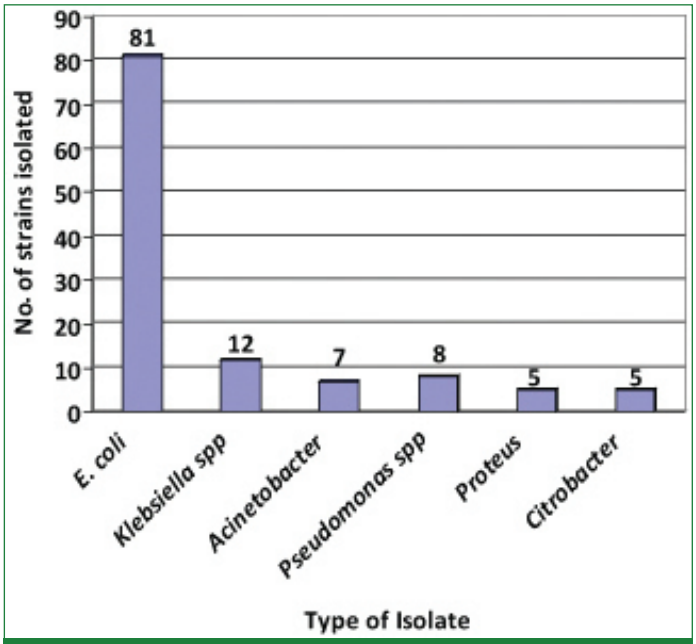
RESULTS

A total of 260 urine samples of the patients with a diagnosis of UTI were included in the study. Among these, 118 samples which showed growth of significant colony count of one organism were considered for study. Of these 118 patients with significant growth of organisms, 62 (52.5%) were female and 56 (47.5%) were male. Majority of the isolates were obtained from the age group of 31-40 years followed by 21-30 years [Table/Fig-2].



[Table/Fig-2]: Distribution of number of isolates according to the age of the patients.

Out of the positive isolates, 81 (68.6%) were *E. coli*, 12 (10.16%) were *Klebsiella* spp., 7 (5.93%) were *Acinetobacter* spp, 8 (6.77%) were *Pseudomonas* spp., 5 (4.23%) were *Proteus* spp, and 5 (4.23%) were *Citrobacter* [Table/Fig-3]. The sensitivity pattern of these bacteria to various antibiotics is shown in [Table/Fig-4]. Among the 81 isolates of *E. coli*, high rate of resistance was seen to amoxicillin, cephalosporins, ciprofloxacin, and nalidixic acid. All the 81 (100%) isolates were susceptible to fosfomycin [Table/Fig-4].



[Table/Fig-3]: Distribution of different bacterial species in subjects with uncomplicated UTI.

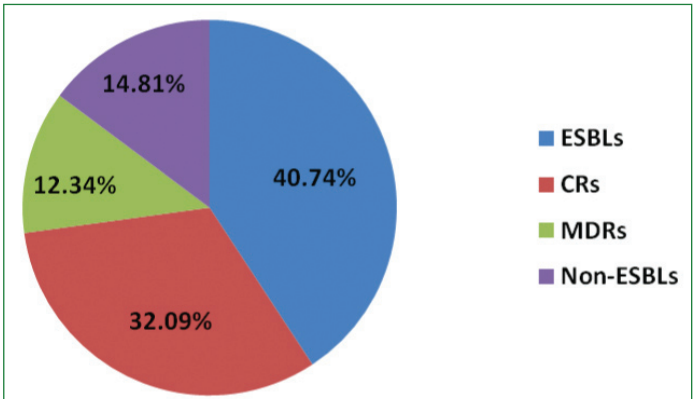
Among 81 *E. coli* isolates, 33 were ESBL producers, 26 were CR, 10 were MDR and the remaining 12 isolates were found to be non-ESBL strains [Table/Fig-5]. All the isolates were found to be susceptible to fosfomycin by Kirby-Bauer disc diffusion method and by E-test method.

DISCUSSION

Appropriate empirical therapy can be determined based on the knowledge of the common causative pathogens of UTIs including local susceptibility patterns. In the present study, 81 (68.6%) out of 118 isolates were *E. coli*. Sultan A et al., also reported similar findings in their study [11]. ESBL-producing *E. coli* are the significant cause of increased morbidity in patients with UTI. They are resistant to penicillins, cephalosporins, and monobactams and can also develop coresistance to other classes of antimicrobial agents like fuoroquinolones, cotrimoxazole, tetracyclines, and aminoglycosides [12]. Co-resistance between nitrofurantoin and fuoroquinolones in urinary isolates of *E. coli* has also been noted [13]. In this study, 40.74% of *E. coli* isolates were ESBL producing. The alternative

Antibiotics	*E.coli* (81)		*Klebsiella* spp (12)		*Acinetobacter* spp (7)		*Pseudomonas* spp (8)		*Proteus* spp (5)		*Citrobacter* spp (5)	
	S	R	S	R	S	R	S	R	S	R	S	R
Amoxicillin	0 (0%)	81 (100%)	0 (0%)	12 (100%)	0 (0%)	7 (100%)	0 (0%)	8 (100%)	0 (0%)	5 (100%)	0 (0%)	5 (100%)
Gentamicin	59 (72.83%)	22 (27.16%)	7 (58.33%)	5 (41.66%)	6 (85.71%)	1 (14.28%)	5 (62.5%)	3 (37.5%)	4 (80%)	1 (20%)	3 (60%)	2 (40%)
Cephalexin	0 (0%)	81 (100%)	0 (0%)	12 (100%)	0 (0%)	7 (100%)	0 (0%)	8 (100%)	0 (0%)	5 (100%)	0 (0%)	5 (100%)
Cefotaxime	0 (0%)	81 (100%)	0 (0%)	12 (100%)	0 (0%)	7 (100%)	0 (0%)	8 (100%)	0 (0%)	5 (100%)	0 (0%)	5 (100%)
Ceftazidime	0 (0%)	81 (100%)	0 (0%)	12 (100%)	0 (0%)	7 (100%)	0 (0%)	8 (100%)	0 (0%)	5 (100%)	0 (0%)	5 (100%)
Cefoperazone-sulbactam	33 (40.74%)	48 (59.25%)	2 (16.66%)	10 (83.33%)	1 (14.28%)	6 (85.71%)	3 (37.5%)	5 (62.5%)	4 (80%)	1 (20%)	3 (60%)	2 (40%)
Cefepime	8 (9.87%)	73 (90.12%)	0 (0%)	12 (100%)	0 (0%)	7 (100%)	1 (12.5%)	7 (87.5%)	0 (0%)	5 (100%)	2 (40%)	3 (60%)
Ciprofloxacin	17 (20.98%)	64 (79.01%)	2 (16.66%)	10 (83.33%)	2 (28.57%)	5 (71.42%)	3 (37.5%)	5 (62.5%)	2 (40%)	3 (60%)	3 (60%)	2 (40%)
Fosfomycin	81 (100%)	0 (0%)	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Imipenem	55 (67.90%)	26 (32.09%)	7 (58.33%)	5 (41.66%)	2 (28.57%)	5 (71.42%)	4 (50%)	4 (50%)	4 (80%)	1 (20%)	3 (60%)	2 (40%)
Nalidixic acid	17 (20.98%)	64 (79.01%)	2 (16.66%)	10 (83.33%)	1 (14.28%)	6 (85.71%)	1 (12.5%)	7 (87.5%)	3 (60%)	2 (40%)	0 (0%)	5 (100%)
Nitrofurantoin	77 (95.06%)	4 (4.93%)	11 (91.66%)	1 (8.33%)	6 (85.71%)	1 (14.28%)	6 (75%)	2 (25%)	0 (0%)	5 (100%)	4 (80%)	1 (20%)
Polymixin B	77 (95.06%)	4 (4.93%)	12 (100%)	0 (0%)	6 (85.71%)	1 (14.28%)	7 (87.5%)	1 (12.5%)	0 (0%)	5 (100%)	3 (60%)	2 (40%)

[Table/Fig-4]: Susceptibility of isolated bacteria to different antibiotics.
S: Sensitive; R: Resistant; NT: Not tested



[Table/Fig-5]: Distribution of resistant *E. coli* isolates.

treatment for ESBLs producing *E. coli* include carbapenems, amikacin, and β-lactam/β-lactamase inhibitor combinations (BL/BLI). But, all these drugs are to be administered parenterally. Additionally, carbapenems and amikacin are associated with nephrotoxicity. Increased usage of carbapenems against *E. coli* infections has lead to the production of carbapenemases, mostly mediated by bla_{OXA48} [14], bla_{NDM} and bla_{VIM} genes [15]. The present study showed 32.09% of *E. coli* isolates were CR. Published literature suggested that fosfomycin might be an effective antibiotic against ESBL-producing, CR, and MDR strains of *E. coli* [16,17].

Fosfomycin, a phosphonic acid derivative, was discovered in Spain in 1969 from cultures of *Streptomyces* spp. [18]. It inhibits cell wall formation by binding to enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), and inhibits formation of the cell wall precursor N-acetylmuramic acid. It is available both orally as well as systemically. When given orally, it is best absorbed if given before food intake. Majority of the drug is excreted unchanged in urine with very high concentration levels achieved in urine (2000 µg/mL) after a single oral dose. Urine levels remain high for prolonged period (over 24 hours) which makes it a suitable drug in the treatment of UTI. Resistance rate is low and most frequently acquired by chromosomal mutations that do not spread easily. Due to its unique chemical structure and mechanism of action, fosfomycin lacks cross-resistance with other antimicrobial agents and can be administered safely in combination with many other antibiotics [6].

The present study has found that fosfomycin is a reliably active antimicrobial drug against ESBL producing and CR *E. coli* showing the susceptibility rate of 100% by both disk diffusion and E-test strip methods. Similar and comparable results have been presented by other studies [Table/Fig-6] [16,17,19-22]. Recent reports show very encouraging in-vitro activity of fosfomycin against MDR gram negative pathogens [Table/Fig-6] [11,16,19,23]. In this study, 12.34% of *E. coli* isolates were MDR and all of them showed 100% sensitivity to fosfomycin.

Studies	ESBLs	Studies	CRs	Studies	MDRs
Patel B et al., [17]	94.4%	Patel B et al., [17]	91.6%	Mittal S et al., [23]	100%
Banerjee S, et al., [16]	97.8%	Banerjee S, et al., [16]	87.5%	Banerjee S et al., [16]	96.6%
Sahni RD et al., [19]	81%	Amladi AU et al., [21]	98.7%	Sahni RD et al., [19]	75.7%
Gupta V et al., [20]	100%	Livermore DM et al., [22]	100%	Sultan A et al., [11]	100%
Present study	100%	Present study	100%	Present study	100%

[Table/Fig-6]: Susceptibility comparison of fosfomycin (%) to ESBL-producing, CR, and MDR strains of *E. coli* in various studies.

Despite of these reports of high percentage of in-vitro susceptibility of fosfomycin, antibiotic susceptibility profile varies not only from time to time but also from one geographical place to another. Though the present study data supported fosfomycin as the drug of choice, few studies done in India and elsewhere observed increased rate of fosfomycin resistance among ESBL-producing, CR, and MDR strains of *E. coli* ranging from 12% to 25% [17,19,24,25]. Therefore, judicious use of fosfomycin in clinical practice is warranted.

Limitation(s)

The present study determined in-vitro susceptibility of fosfomycin against limited number of ESBL-producing, CR, and MDR strains of *E.coli.* Future studies must put more emphasis on the analysis of fosfomycin resistance genes which is very important to prevent quick spread of MDR strains of *E.coli*.

CONCLUSION(S)

Fosfomycin is a bactericidal agent showing high in-vitro activity against common uropathogens, especially *E. coli*. It has low level of resistance as compared to other antibiotics. Antimicrobial activity of fosfomycin, especially against MDR isolates, makes it an effective and safe drug in the treatment of UTIs. Determination of MIC to fosfomycin is necessary for the detection of resistance. For *E.coli*, surveillance for resistance to fosfomycin in routine susceptibility testing should be included. Finally, availability of oral preparations of fosfomycin gives an opportunity to promote switching from Intravenous (IV) fosfomycin to oral therapy and potentially reduce duration of hospital stay, healthcare costs and risk of complications related to IV access.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jun 06, 2020
- Manual Googling: Sep 21, 2020
- iThenticate Software: Dec 26, 2020 (18%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jun 05, 2020**
Date of Peer Review: **Jul 18, 2020**
Date of Acceptance: **Sep 22, 2020**
Date of Publishing: **Jan 01, 2021**