Original Article

Fosfomycin susceptibility among multidrug-resistant, extended-spectrum beta-lactamase-producing, carbapenem-resistant uropathogens

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ABSTRACT

Introduction: Urinary tract infection (UTI) is one of the most common infectious diseases. With the emergence of multidrug resistance (MDR), therapeutic options for treatment of UTIs are becoming limited. Fosfomycin has emerged as a novel oral therapeutic option with bactericidal activity against the MDR uropathogens. We evaluated the susceptibility pattern of uropathogens to this antibiotic.

Methods: A prospective study was conducted for 6 months in a tertiary care hospital in Eastern India to evaluate whether the common uropathogens were susceptible to fosfomycin. Identification of organisms causing significant bacteriuria was done by conventional biochemical and VITEK 2 Compact System™. Antimicrobial susceptibility testing was performed against these pathogens by Kirby-Bauer disc diffusion method. Minimum inhibitory concentrations were measured for certain drugs by E-strips and VITEK 2 Compact System.

Results: A total of 2229 urine samples were referred for culture during the study period, which yielded 356 significant bacterial isolates. Among these isolates, 64.78% were extended-spectrum beta-lactamases producers, 15.97% were carbapenem-resistant *Enterobacteriaceae,* and 42.7% isolates were found to be MDR *Enterobacteriaceae* (MDRE). However, 95.18% of the total isolates and 95.93% of MDRE were found to be susceptible to fosfomycin.

Conclusion: The common uropathogens, including MDR isolates, show high *in vitro* susceptibility to fosfomycin, which therefore has the potential to emerge as a promising alternative oral agent for outpatient therapy of UTIs.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common clinical entities encountered by the medical practitioners. The most common organisms causing UTI are all known to harbor multiple drug resistance (MDR) mechanisms, both inherited or transmissible and chromosomal or extrachromosomal against the commonly used oral antimicrobial agents for UTI caused by Gram-negative organisms, i.e., fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and second and third-generation cephalosporins.[1] With rampant overuse and abuse of these drugs, particularly in the developing countries like India with availability of over the counter drugs, Gram-negative organisms have become overwhelmingly resistant to all or most of these agents, making outpatient oral therapy increasingly difficult.

Extended spectrum beta-lactamase (ESBL) production is common among clinical isolates of *Enterobacteriaceae*. Since carbapenems are considered drug of choice for serious infections caused by these microorganisms, use of these drugs is increasing, which is contributing to the selection and spread of carbapenem-resistant Gram-negative bacilli.[2] Various definitions are given for MDR organisms. The most commonly used definition is bacteria which is resistant to three or more antimicrobial classes.[3]

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Fosfomycin is an oral antibiotic with bactericidal activity against these MDR pathogens. It inhibits synthesis of the bacterial cell wall.[4] It is best absorbed if given before food intake and is excreted in urine.[5] It achieves high concentration in urine of 2000 μg/ml and maintains high levels for over 24 h.[6] Hence, single-time oral therapy with fosfomycin has been recommended in uncomplicated UTI.[7]

This study was done with the objective to determine *in vitro* fosfomycin susceptibility of common uropathogens and determining the resistance pattern of these organisms against commonly prescribed antimicrobial agents.

METHODS

A prospective study was conducted from November, 2015, to April, 2016 in the Department of Microbiology in a 380 bedded tertiary care hospital and medical college in Eastern India. Urine samples were collected from patients who had clinical features suggestive of UTI from the inpatients and outpatients departments. Freshly collected mid-stream clean catch urine samples were collected from the non-catheterized, alert, conscious, adult patients with indications for urine culture as assessed by the clinicians from the various departments.[8] Surgically collected urine samples and suprapubic aspirates were collected from some patients as indicated. If the patients were catheterized; then, urine samples were collected from the catheter with proper surgical asepsis with needle and syringe as described in erstwhile standard technique guidelines.[9]

The urine samples were processed immediately (within 30 min) after collection. Direct microscopy of the uncentrifuged urine sample was done, and pus cells and bacteria were noted. Centrifuged deposits were examined under microscope for the casts and crystals. The urine samples were plated by semi-quantitative method on blood agar and MacConkey agar and incubated at 37°C overnight and if required, till 48 h. The growth of organisms and colony count were taken. The isolates obtained from the samples with significant bacteriuria in the background of relevant supportive clinical features of UTI and/or the presence of significant pus cells on direct microscopy, as described in the standard guidelines, were only included in the study.[1]

The identification of the organism was done by conventional biochemical tests and VITEK 2 Compact System (BioMérieux Inc., France). The antimicrobial susceptibility was performed for these isolates on Mueller-Hinton agar plates by Kirby-Bauer disc diffusion method and interpreted according to the Clinical and Laboratory Standards Institute guidelines M100-S25 version published in 2015.[10] The different antimicrobial agents that were tested for different organisms are given in Table 1. For *Enterobacteriaceae* other than *E. coli,* minimum inhibitory concentration (MIC) testing was done for fosfomycin by E-test for confirmation, and interpretation was done according to EUCAST guidelines 2015 as given by Falagas *et al*.[4] As per the previously published guidelines, cefazolin susceptibility can be used to predict the susceptibility toward all oral cephalosporins when used for treating uncomplicated UTIs caused by *E. coli*, *Klebsiella* spp., and *Proteus mirabilis*.[10] For detection of ESBL producers, screening was done using disc diffusion method with ceftriaxone and cefotaxime, and confirmation was done by simultaneous testing with cefotaxime (30 μg) and combination of cefotaxime/clavulanate (30/10 μg) by disc diffusion method. Modified Hodge test was done for the confirmation of the carbapenem-resistant *Enterobacteriaceae*.[10]

MDR *Enterobacteriaceae* (MDRE) are the organisms resistant to any three different classes of antibiotics as defined by the previous guidelines.[3] In our study, it includes resistance to any three of the following groups - cephalosporins, fluoroquinolones, aminoglycosides, folate pathway inhibitors (trimethoprim-sulfamethoxazole), and nitrofurantoin.

RESULTS

A total of 2229 urine samples were received fulfilling the inclusion criteria. Among these, 345 samples showed growth of significant colony count of one or two organisms, yielding a sum of 356 isolates fulfilling the criteria for significance.

Of these 345 patients with significant growth of organisms, 92 (26.67%) were male and 253 (73.33%) were female. 16 (4.63%) were children below 12 years of age. Out of the positive isolates, 147 were from OPD, 206 from inpatient wards, and 3 from the ICU [Table 2]. There were 216 (60.67%) isolates of *E. coli*, 67 (18.82%) isolates of *K. pneumoniae*, 15 (4.21%) isolates of *Pseudomonas* spp., 44 (12.35%) isolates of *Enterococcus* spp.

Among the 216 isolates of *E. coli*, high rate of resistance was seen to cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole. All 216 (100%) were susceptible to colistin, and 212 (98.14%) were susceptible to fosfomycin [Table 3]. Among the 67 isolates of *K. pneumoniae*, the majority were resistant to cephalosporins and fluoroquinolones. All 67 (100%) were susceptible to colistin, and 64 (95.52%) isolates were susceptible to fosfomycin.

Among the 15 isolates of *Pseudomonas* spp. there were 13 isolates of *Pseudomonas aeruginosa* and 2 isolates *Pseudomonas putida*. All 15 (100%) were resistant to ceftazidime. High resistance rates were seen against ciprofloxacin and levofloxacin, and none were resistant to colistin [Table 3]. Among the 44 *Enterococcus* spp., high resistance was seen against ampicillin, ciprofloxacin, levofloxacin, and high-level gentamicin. Only 1 (2.27%) was

Table 1: The different antimicrobial agents tested for susceptibility

Enterobacteriaceae (μg)	NFGNB (μg)	*Enterococcus* (μg)
Cefazolin (30)	-	Ampicillin (10)
Ceftriaxone (30)	Ceftazidime (30)	-
Cefotaxime (30)	Cefepime (30)	-
Amoxicillin-clavulanate (20/10)	Piperacillin-tazobactam (100/10)	-
Ciprofloxacin (5)	Ciprofloxacin (5)	Ciprofloxacin (5)
Levofloxacin (5)	Levofloxacin (5)	Levofloxacin (5)
Trimethoprim-Sulfamethoxazole (1.25/23.75)	-	-
Nitrofurantoin (300)	-	Nitrofurantoin (300)
Amikacin (30)	Amikacin (30)	-
Gentamicin (10)	Gentamicin (10)	High-level gentamicin (120)
Meropenem (10)	Meropenem (10)	Vancomycin (30)
Imipenem (10)	Imipenem (10)	Teicoplanin (30)
Colistin (10)	Colistin (10)	Linezolid (30)
Fosfomycin (200)	Fosfomycin (200)	Fosfomycin (200)

NFGNB=Nonfermenting Gram-negative bacilli

Table 2: The distribution of organisms from outpatient, ward, Intensive Care Unit

Organism	OPD	Ward	ICU	Total
E. coli	110	106	0	216
K. pneumoniae	22	44	1	67
Enterobacter spp.	0	1	0	1
Citrobacter spp.	0	1	0	1
P. mirabilis	1	0	0	1
M. morganii	1	0	0	1
Budvicia spp.	0	1	0	1
Pseudomonas spp.	4	9	2	15
A. baumannii complex	0	6	0	6
B. cepacia	0	1	0	1
Enterococcus spp.	9	35	0	44
S. saprophyticus	0	2	0	2
Total	147	206	3	356

ICU=Intensive Care Unit, OPD=Outpatients department, *E. coli*= *Escherichia coli*, *K. pneumoniae*= *Klebsiella pneumoniae*, *P. mirabilis*= *Proteus mirabilis*, *M. morganii*= *Morganella morganii*, *A. baumannii*=*Acinetobacter baumannii*, *B. cepacia*= *Burkholderia cepacia*, *S. saprophyticus*= *Staphylococcus saprophyticus*

resistant to fosfomycin, and all (100%) were susceptible to vancomycin, teicoplanin, and linezolid. The *Staphylococcus* isolates were not tested for fosfomycin susceptibility.

There were total 284 isolates of *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Among these 184 (64.78%) were ESBL producers, of which 137 were *E. coli* and 47 were *K. pneumoniae* and 100 (35.21%) were non-ESBL producers, of which 79 were *E. coli*, 20 were *K. pneumoniae*, and one *P. mirabilis* [Table 4]. Among 288 *Enterobacteriaceae* isolates, 45 (15.62%) were carbapenem-resistant *Enterobacteriaceae*, and 123 (42.7%) isolates were found to be MDRE.

Among the total isolates tested for susceptibility, 337 (95.18%) out of 354 were found to be fosfomycin susceptible, 95.93% of MDRE [Table 5] and 89.13% of CRE [Table 6] were found to be susceptible to fosfomycin (MIC range for fosfomycin was 0.25–512 μg/ml). The MIC_{90} and MIC_{50} of fosfomycin for *Enterobacteriaceae* were found to be 8 and 2 μg/ml, respectively. The MIC_{90} and MIC_{50} of fosfomycin for *K. pneumoniae* were found to be 8 and 2 μg/ml, respectively. There was only one *Enterobacter* with MIC of 1 μg/ml. Fosfomycin resistance were found among 4 isolates of *E. coli*, 3 *K. pneumoniae*, 4 *Pseudomonas* spp., 3 *A. baumannii* complex, and one isolate each of *M. morganii*, *B. cepacia*, and *Enterococcus* spp.

DISCUSSION

Fosfomycin is a novel antibiotic with good *in vitro* activity against the common pathogens causing UTI, particularly toward the *Enterobacteriaceae*. Fosfomycin is active against both Gram-negative and Gram-positive pathogens, including *Entererococcus* spp., *Staphylococcus aureus*, *E. coli*, *Salmonella* spp., *Shigella* spp., *Klebsiella*, *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., and *P. mirabilis*.[4] The activity of fosfomycin was evaluated as early as 1997 by Dastidar *et al*. Fosfomycin was found to possess somewhat lower activity against *Staphylococcus aureus* compared with other penicillins; however, it showed powerful activity toward *E. coli*, *Klebsiella* spp., and *P. mirabilis*.[11] In a study done by Gupta *et al*. from Chandigarh, among 150 uropathogenic strains of *E. coli*, 52.6% of isolates were ESBL producers, and all strains were susceptible to fosfomycin.[12] In another study by Mittal *et al*., it was found that fosfomycin was 100% sensitive to uropathogenic *E. coli* strains.[13] In this present study, 95.18% isolates were susceptible to fosfomycin which is similar to the findings of a study done by Sabharwal and Sharma where it was found that 94.4% of the isolates causing UTI were susceptible to fosfomycin.[14] Khawaja *et al*. found that after oral therapy with fosfomycin bacterial eradication was seen in 96.3% patients.[15] There is also a report of a person who returned to Canada after hospitalization in India with a resistant metallo-beta-lactamase-producer strain who was successfully treated with ertapenem and fosfomycin.[16] In a study done by Rajenderan *et al*., it was found that fosfomycin was the only antibiotic that effectively inhibited

Table 3: The susceptibility of isolated organisms to different antibiotics

Antibiotic	*E. coli* (*n*=216) (%)	*K. pneumoniae* (*n*=67) (%)	*Pseudomonas* spp. (*n*=15) (%)	*Acinetobacter* spp. (*n*=6) (%)	*Enterococcus* spp. (*n*=44) (%)	*P. mirabilis*	*M. morganii*	*Enterobacter spp.*	*Citrobacter spp.*	*Budvicia spp.*	*B. cepacia*
Ampicillin	NA	NA	NA	NA	3 (6.82)	NA	NA	NA	NA	NA	NA
Cefazolin	69 (31.94)	17 (25.37)	NA	NA	NA	S	R	R	R	R	NA
Ceftriaxone	79 (36.57)	20 (29.85)	NA	NA	NA	S	R	R	R	R	NA
Cefotaxime	79 (36.57)	20 (29.85)	NA	NA	NA	S	R	R	R	R	NA
Ceftazidime	NA	NA	0	2 (33.33)	NA	NA	NA	NA	NA	NA	R
Cefepime	NA	NA	10 (66.67)	2 (33.33)	NA	NA	NA	NA	NA	NA	R
Amoxicillin-clavulanate	70 (32.41)	12 (17.91)	NA	NA	NA	R	S	S	R	R	NA
Piperacillin-tazobactam	NA	NA	9 (60)	2 (33.33)	NA	NA	NA	NA	NA	NA	S
Ciprofloxacin	89 (41.2)	25 (37.31)	6 (40)	3 (50)	5 (11.36)	S	S	R	R	R	R
Levofloxacin	108 (50)	27 (40.3)	7 (46.67)	3 (50)	7 (15.91)	S	S	R	R	R	R
Trimethoprim-sulfamethoxazole	104 (48.15)	32 (47.76)	NA	NA	NA	S	R	IS	R	R	S
Nitrofurantoin	170 (78.7)	30 (44.78)	NA	NA	34 (77.27)	IS	R	S	R	R	NA
Amikacin	184 (85.19)	45 (67.16)	11 (73.33)	3 (50)	NA	S	S	S	R	R	R
Gentamicin	182 (84.26)	45 (67.16)	11 (73.33)	3 (50)	15 (34.09)	S	S	S	R	R	R
Meropenem	192 (88.89)	46 (68.66)	5 (33.33)	1 (16.67)	NA	S	S	S	R	S	R
Imipenem	192 (88.89)	46 (68.66)	5 (33.33)	1 (16.67)	NA	S	S	S	R	S	R
Colistin	All (100)	All (100)	All (100)	All (100)	NA	R	R	S	S	S	NA
Fosfomycin	212 (98.14)	64 (95.52)	11 (73.33)	3 (50)	43 (97.72)	S	R	S	S	S	R
Vancomycin	NA	NA	NA	NA	44 (100)	NA	NA	NA	NA	NA	NA
Teicoplanin	NA	NA	NA	NA	44 (100)	NA	NA	NA	NA	NA	NA
Linezolid	NA	NA	NA	NA	44 (100)	NA	NA	NA	NA	NA	NA

S=Susceptible, IS=Intermediate susceptible, R=Resistant, NA=Not applicable, *B. cepacia*=*Burkholderia cepacia*, *E.coli*=*Escherichia coli*, *K. pneumoniae*=*Klebsiella pneumoniae*, P. mirabilis=Proteus mirabilis and M. morganii=Morganella morganii. Enterococcus High level gentamicin was tested

Table 4: Fosfomycin sensitivity among extended spectrum beta-lactamase producers and non-extended-spectrum beta-lactamase producers

Organism	ESBL producer (%)	Non-ESBL producer (%)
E. coli	134/137 (97.81)	78/79 (98.74)
K. pneumoniae	44/47 (93.61)	20/20 (100)
P. mirabilis	0	1/1 (100)
Total	178/184 (96.74)	99/100 (99)

ESBL=Extended-spectrum-beta lactamase, *E. coli*=*Escherichia coli*, *K. pneumoniae*=*Klebsiella pneumoniae*, *P. mirabilis*=*Proteus mirabilis*

Table 5: Fosfomycin sensitivity among multidrug-resistant *Enterobacteriaceae*

Organism	MDRE (%)	Non-MDRE (%)
E. coli	86/89 (96.62)	126/127 (99.21)
K. pneumoniae	30/32 (93.75)	34/35 (97.14)
Others	2/2 (100)	2/3 (66.67)
Total	118/123 (95.93)	162/165 (98.18)

E. coli=*Escherichia coli*, *K. pneumoniae*=*Klebsiella pneumoniae*, MDRE=Multidrug-resistant *Enterobacteriaceae*

Table 6: Fosfomycin sensitivity among carbapenem-resistant *Enterobacteriaceae*

Organism	CRE (%)	Non-CRE (%)
E. coli	21/24 (87.5)	191/192 (99.48)
K. pneumoniae	19/21 (90.47)	45/46 (97.82)
Others	1/1 (100)	3/4 (75)
Total	41/46 (89.13)	239/242 (98.76)

E. coli=*Escherichia coli*, *K. pneumoniae*=*Klebsiella pneumoniae*, CRE=Carbapenem-resistant *Enterobacteriaceae*

90% of the strains of *E. coli* and *Klebsiella* spp.[17] Sahni *et al*. stated that fosfomycin susceptibility was found in 83% *E. coli* and 90% *Enterococcus* spp. and 47.6% were ESBL producers.[18] *M. morganii* is resistant to fosfomycin[4] as shown in this study also.

In our study, 98.14% of *E. coli*, 95.52% *K. pneumoniae*, and 97.72% *Enterococcus* spp. were susceptible to fosfomycin. Among the ESBL producing *Enterobacteriaceae*, 96.74% isolates were found to be susceptible to fosfomycin. The susceptibility among carbapenem-resistant *Enterobacteriaceae* was also found to be quite high, at 89.13%, which is really encouraging in the grim scenario of more commonly prescribed nephrotoxic polymyxins as the salvage therapy for these cases. Following the standard definitions accepted,[3] our study revealed about 42.7% MDRE isolates. Out of the total of 123 MDRE isolates, which were resistant to at least three (or more) groups of antibiotics, 118 (95.93%) were susceptible to fosfomycin.

The most frequent Gram-positive uropathogen encountered in our study was *Enterococcus* spp., which were found to be highly susceptible (97.72%) to fosfomycin. These findings also corroborate to that of Sultan *et al*., who found that fosfomycin was effective in 100% of methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, ESBL, high-level aminoglycoside resistance, and overall, susceptibility to fosfomycin in AmpC producers was also extremely high.[19] Marie *et al*. reported that fosfomycin and colistin were the two most effective antimicrobial agents.[20] Despite of these reports of high percentage of *in vitro* susceptibility of fosfomycin, it was by far an underprescribed antimicrobial agent in India as well as in many parts of the world. It is also an underrated agent for complicated UTI cases though urinary concentration and safety profile is way above many other commonly prescribed antibiotics for the MDRE[21] and CRE pathogens.

Limitations

This study was done for the evaluation of *in vitro* activity of fosfomycin and not a clinical evaluation of efficacy. There were very few *Enterobacteriaceae* isolates other than *E. coli* and *K. pneumoniae* found in the study.

CONCLUSION

Fosfomycin is shown to have high *in vitro* activity against common uropathogens, including MDR isolates, ESBL producers, and carbapenem-resistant *Enterobacteriaceae*. It has a high potential to emerge as a promising and safe alternative oral agent for both outpatient and inpatient therapy of UTIs, particularly in countries, where its prescription habits among clinicians are scarce. However, further studies are needed to evaluate the various *in vitro* phenotypic and genotypic profiles of fosfomycin resistance among uropathogens.

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