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Original Research Article

In-Vitro Antibiotic Susceptibility of Urinary *Enterobacterales* and *Enterococcus* Isolates with Special Reference to Fosfomycin Susceptibility

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Abstract:

Introduction: With the emergence of multidrug resistance and increasing use of high-level antibiotics risking the emergence of resistance, effective antibiotics that help in conserving these higher drugs for more severe infections are the need of the time.

Aims and objectives: To study the susceptibility pattern of *Enterobacterales* and *Enterococcus* species against commonly prescribed urinary antimicrobial agents and fosfomycin and to compare the susceptibility pattern in extended spectrum beta-lactamases (ESBL), multidrug-resistant *Enterobacterales* (MDR) and carbapenem resistant *Enterobacterales* (CRE's).

Materials and Methods: This prospective, cross-sectional study was carried out in the department of Microbiology of a tertiary care hospital over a period of six months between July 2021 to December 2021. 225 consecutive non-duplicate isolates of *Enterobacterales* (n=188) and *Enterococcus* species (n=37) recovered from suspected cases of UTI were included. Antimicrobial susceptibility test was carried out using the Kirby Bauer disc diffusion method.

Results: Out of 188 isolates of *Enterobacterales*, 102 were *Escherichia coli* (45.3%), 73 were *Klebsiella pneumoniae* (32.4%) and 13 (5.78%) belonged to other Enterobacterale species. Among 37 isolates of *Enterococcus species*, 21/37 were *E. fecalis* and 16/37 were of *E. faecium* group. In *E. coli*, susceptibility to the other antibiotics tested ranged from 9.8% to 85.29%. In *K. pneumoniae*, susceptibility to all antibiotics was lower than E. coli. The susceptibility to fosfomycin in *Enterobacterales* and in *Enterococcus* isolates was 85.1% and 97.30%. One *E. faecium* species was resistant. *E. coli* were more susceptible (98%) as compared to *K. pneumoniae* (65.75%). ESBL producers were more susceptible than non- ESBL producers, but the difference was not statistically significant. The susceptibility to fosfomycin among non-CRE isolates was significantly higher than in CRE isolates (93.86% versus 71.62%).

Conclusion: Fosfomycin with its ease of dosage and high susceptibility against *Enterobacterales* and *Enterococcus* species, is a good choice of antibiotic for UTI and can be prescribed to both out as well as indoor patients with expected favorable outcomes.

Keywords: Antibiotic susceptibility, urinary *Enterobacterales, Enterococcus* species, Fosfomycin susceptibility, multidrug resistant enterobacterales

Introduction

Urinary tract infections (UTI) cause 40% of bacterial infections globally of which 10-20% are hospital related and rest are in community. [1] In a study from Mumbai, prevalence of UTI has been reported as 34.5% and 36.68%. [2] *E. coli, K. pneumoniae* and *P.aeruginosa* are the most common bacterial pathogens isolated from the urinary tracts of infected patients. [3] These organisms demonstrate multiple drug resistance mechanisms against the commonly used oral antimicrobial agents.

With a rising prevalence of extended spectrum beta lactamases (ESBL) and carbapenem resistant Enterobacterales (CRE) and multidrug resistance (MDR), infections have become refractory to treatment leading to serious outcomes and higher cost of treatment. [2,4] Emergence of vancomycin resistance is also being increasingly reported in *Enterococcus* species. [5] Routine periodic surveillance of antimicrobial susceptibility pattern (AMST) is essential for defining empiric therapy. [1]

Fosfomycin, which is an old drug, has been recently reported to have bactericidal activity against these MDR pathogens in cases of UTI. [6] It is a bactericidal drug which is a phosphoenolpyruvate (PEP) analogue that interferes with the synthesis of cell

wall of both Gram negative and Gram positive bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase. [2,7] It is available in three forms – fosfomycin trometamol which is synthetically derived and fosfomycin calcium which are both oral forms, and fosfomycin disodium which is intravenous.

Oral fosfomycin is mainly used in the treatment of urinary tract infections, particularly those caused by *E. coli* and *E. faecalis*. It is excreted non-metabolized in the urine in high concentrations and maintains high level for over 24 hours. Thus, it can be given as a single oral dose which also improves patient compliance and can be given on an outpatient basis. [7] It is well tolerated, with a low incidence of adverse events. Its urinary concentration and safety profile are higher compared to commonly prescribed antimicrobials for MDRE and CRE pathogens and is also recommended in pregnancy. [8] Following a single 3-g oral dose of fosfomycin trometamol, peak urine concentrations are reached within 4 hours. High urine as well as bladder tissue concentrations (128 mg/liter) are retained for 1 to 2 days, which is sufficient to eliminate the majority of common uropathogens.

This study was conducted with the primary aim of determining the in-vitro susceptibility of *Enterobacterales* and *Enterococcus* species isolated from cases of suspected UTI against the commonly prescribed urinary antimicrobial agents, with special reference to fosfomycin. This study also tried to evaluate fosfomycin susceptibility among drug resistant subsets which included extended spectrum beta-lactamases (ESBL), multidrug-resistant *Enterobacterales* (MDRE) and carbapenem resistant E*nterobacterales* (CRE) including metallo-betalactamases (MBL).

Materials and Methods

This prospective, cross sectional study was carried out in the Department of Microbiology of a tertiary care teaching hospital in Mumbai over a period of six months (from July 2021 to December 2021). Institutional ethics committee (IEC) permission was obtained prior to initiation (EC/111/2021).

A total of 225 consecutive, non-duplicate isolates of *Enterobacterales* (n=188) and *Enterococcus* species (n=37) considered as pathogens from samples received in the laboratory were included.

Inclusion Criteria: Isolates recovered from freshly collected midstream urine specimens from adults >= 18 years age received on an outpatient basis or from patients admitted in the hospital with suspected UTI were included.

Exclusion Criteria: Specimens demonstrating polymicrobial growth (>2 morphotypes), those demonstrating non-significant growth (Colony count $<10^5$ CFU/ml of urine), samples from patients with no symptoms suggestive of UTI and those received from children <18 years were excluded.

Freshly collected urine specimens were immediately processed upon receipt (i.e. within 2 h). A Gram's stain of uncentrifuged specimen was carried out and presence and number of pus cells and bacteria were noted. Using all aseptic measures, these were simultaneously streaked on 5% sheep blood agar (SBA) and MacConkey agar plates for semi-quantitative culture using a standard loop calibrated for 0.001 ml of urine. Detection of ≥100 colonies on the streak lines on SBA after 18-24 hours of incubation was considered significant and corresponded to a colony count of $\geq 10^5$ CFUs/ ml. The organisms were identified up to the species level using standard microbiological procedures. [9,10]

Susceptibility to antimicrobial agents was determined by Kirby-Bauer disc diffusion method on Mueller-Hinton agar as per Clinical and Laboratory Standards Institute (CLSI) 2021. [11] Antibiotics tested were amikacin, amoxicillin-clavulanate, cefazolin, ceftazidime, ceftriaxone, ciprofloxacin, co-trimoxazole, fosfomycin, gentamicin, imipenem, meropenem, nitrofurantoin & norfloxacin for *Enterobacterales* family and ampicillin, ciprofloxacin, fosfomycin, high level gentamicin, linezolid, nitrofurantoin, norfloxacin, penicillin, teicoplanin, tetracycline & vancomycin for *Enterococcus* species. Antibiotic discs were obtained from HiMedia Laboratories Pvt. Ltd, Mumbai, India which were put into use after undergoing Quality Control testing as per CLSI. [12,13] Quality control for all antibiotic discs was carried out using E. coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853 and Staphylococcus aureus ATCC 25923 for Enterobacterales and Staphylococcus aureus ATCC 25923 for Enterococci as per CLSI before putting into use.

For fosfomycin susceptibility, disc diffusion zone diameter breakpoints for *E. coli* and E. faecalis was interpreted as per CLSI 2021 (≥16mm, susceptible; 13-15 mm intermediate; ≤12mm resistant). For *K.pneumoniae, Enterobacterales* species other than *E. coli* and for *E.faecium*, Lu et al (2011) & Mojica et al (2020) proposed disc diffusion (DD) breakpoints (≥16mm, susceptible; 13-15 mm intermediate; ≤12mm resistant) were used for interpretation as CLSI did not give breakpoints for these organisms. [3] Screening and confirmatory tests for ESBL production was performed and interpreted as per CLSI.

Multi-drug-resistance (MDR) in *Enterobacterales* was defined as non-susceptibility to at least one agent in three or more of 17 antimicrobial categories for *Enterobacterales*.

All isolates of *Enterobacterales* were screened for carbapenemase production by meropenem and/or imipenem disc as per CLSI 2021 M100. Any re-

sistance was considered potentially carbapenem resistant. [11] The suspected CRE isolates were further confirmed for carbapenemase production by mCIM test. mCIM was used to confirm carbapenemase production followed by eCIM which was used to differentiate metallo-β-lactamases from serine carbapenemases in *Enterobacterales.* [11]

Statistical Analysis: Chi square test or Fischer exact test were used for comparison between groups. A p value < 0.05 was considered as statistically significant. Percentages were calculated wherever necessary.

Results

A total of 225 consecutive non-duplicate isolates of *Enterobacterales* (n=188) and *Enterococcus* species (n=37), recovered from urine samples and fulfilling the inclusion criteria were included in the study. The distribution of urinary isolates in the study population is shown in Table 1.

Table 1: Distribution of urinary isolates (n=225)

Organism isolated	Number	Percentage %
Enterobacterales species		
Escherichia coli	102	45.33
Klebsiella pneumoniae	73	32.44
Other *Enterobacterales*	13	5.78
a) *Providencia* species	7	3.11
b) *Enterobacter* species	3	1.33
c) *Proteus mirabilis*	2	0.89
d) *Proteus vulgaris*	1	0.44
***Enterococcus* species**	37	16.44
a) *Enterococcus faecalis*	21	9.33
b) *Enterococcus faecium*	16	7.11
Total	225	100

Table 2: Comparison of antimicrobial susceptibility between *E. coli* and *K. pneumoniae*:

Antibiotic agent	Number of susceptible isolates of *E. coli* (n=102)	Number of susceptible isolates of *K. pneumoniae* (n=65)	p-value
	Susceptible (%)	**Susceptible (%)**	
Fosfomycin	100(98.04)	48(65.75)	**0.00000158***
Imipenem	73(71.57)	34(46.57)	**0.0114***
Meropenem	74(72.55)	33(45.20)	**0.00423***
Amikacin	69(67.65)	31(42.46)	**0.0103***
Gentamicin	61(59.80)	30(41.09)	0.0841
Nitrofurantoin	87(85.29)	24(32.87)	**<0.0000001***
Co-trimoxazole	29(28.43)	20(27.39)	0.7463
Ceftazidime	26(25.49)	19(26.02)	0.5953
Amoxicillin- Clavulanate	49(48.04)	18(24.65)	**0.00890***
Ceftriaxone	15(14.70)	17(23.28)	0.0668
Ciprofloxacin	13(12.74)	15(20.54)	0.0814
Norfloxacin	11(10.78)	14(19.17)	0.0575
Cefazolin	10(9.80)	9(12.32)	0.4225

As described in Table 2, *E.coli* demonstrated better susceptibility as compared to *Klebsiella pneumoniae.* The difference is statistically significant. Susceptibility to fosfomycin was 98.04% and 65.75% in *E.coli* and *Klebsiella pneumoniae* respectively. Susceptibility to commonly used urinary antimicrobials, co-trimoxazole and quinolones was poor.

92.3% (12/13) of other *Enterobacterales* were susceptible to fosfomycin. The highest susceptibility to antimicrobial agents among other *Enterobacterales*, excluding fosfomycin, was observed with meropenem (84.61%), followed by amikacin (76.92%) and ceftazidime (76.92%). Cefazolin displayed the least susceptibility at 38.46%.

In 37 *Enterococcus* species isolates, fosfomycin susceptibility was noted in 97.30% (n=36). All 21 *E. faecalis* isolates and 15/16 (93.75%) *E. faecium* isolates were susceptible to fosfomycin. All *Enterococcus* species isolates were susceptible to linezolid, teicoplanin, and vancomycin, with the lowest susceptibility observed to fluoroquinolones (ciprofloxacin-8.1% and norfloxacin-8.1%).

Amongst 32 ESBL producers identified (23 *E. coli*, 9 *K. pneumoniae*), 90.62% were susceptible to

fosfomycin, compared to 82.98% susceptibility in non-ESBL producers. Although non-ESBL producers displayed lower susceptibility to fosfomycin, the difference was not statistically significant (p=0.1679, CI- 0.5526, 5.178).

All ESBL-producing *E. coli* isolates (23/23) were susceptible to fosfomycin, while susceptibility among non-ESBL strains was 97.46%. In ESBL-producing *K. pneumoniae*, 6 out of 9 isolates (66.66%) were susceptible to fosfomycin, whereas among non-ESBL K. pneumoniae strains, 42 out of 64 (65.62%) showed susceptibility. No ESBLs were isolated in other *Enterobacterales*. Among non-ESBL strains of other *Enterobacterales*, 12 out of 13 (92.30%) were susceptible to fosfomycin. The difference in fosfomycin susceptibility between ESBL-producing *E. coli* and *K. pneumoniae* was statistically significant (p=0.001815).

Out of 167 multi-drug-resistant *Enterobacterales* isolates, 139 (83.23%) were susceptible to fosfomycin.

Fosfomycin susceptibility among carbapenem-resistant *Enterobacterales* (CRE) isolates was 71.62%, whereas among non-carbapenem-resistant isolates, it was 93.86%. This difference was statistically significant (p=0.00001431).

Out of 13 metallo-beta-lactamase (MBL) producers, 84.61% were susceptible to fosfomycin, while among the 15 serine carbapenemase producers, 73.33% were susceptible.

In the present study, fosfomycin susceptibility among isolates recovered from cases in outpatient settings was higher 61/66 (92.42%) as compared to ward patients 130/152(85.33) while in the ICU's, it was the least 5/7(71.43%). Relative risk for developing resistance to fosfomycin in hospitalized patients (ward and ICU) was higher than in outpatients (RR-1.992, LL - 0.756, UL - 4.83).

Discussion

Urinary tract infection is one of the most common infections seen in out-patient settings, predominantly in female patients especially in pregnancy. [14,15] With the rising antimicrobial resistance to commonly used antibiotics and the deficiency of any new ones being added to the armamentarium, the therapeutic options available need to be re-evaluated. With changing antimicrobial resistance patterns over the course of time, antibiograms need to be studied on a regular basis to detect any change in resistance pattern and modify therapeutic policies accordingly. Therefore, this study was conducted keeping this in mind and also evaluating fosfomycin which is an older drug and which has recently been reported as having regained its activity after being out of use for a long time.

This study dealt with *Enterobacterales* and *Enterococcus* species only as majority of urinary tract infections in this hospital are seen to be caused by these groups of organisms. *E.coli* and *Klebsiella pneumoniae* were the predominant isolates.

Among *Enterobacterales*, 160 out of 188 isolates (85.10%) demonstrated susceptibility to fosfomycin. This finding resonates with Sreenivasan et al (Puducherry, 2019) who found that 340 / 392 (86.7%) *Enterobacterales* isolates exhibited similar susceptibility.[6] Sabharwal et al (Jaipur, 2015) observed an even higher susceptibility rate of 94.4% among *Enterobacterales* isolates causing UTIs, as also seen by Banerjee et al (Kolkata, 2016) (337 / 354; 95.54%) surpassing the rate observed here. [16,17] Their study included 216 (60.67%) isolates of *E. coli*, 67 (18.82%) of *K. pneumoniae*, 15 (4.21%) of *Pseudomonas* species, and 44 (12.35%) of *Enterococcus* species. Lu et al (Taiwan, 2011) as well as Kishore et al (2020, Uttarakhand) also demonstrated high susceptibility of *Enterobacterales* species to fosfomycin, with rates of 92.33% and 97.46%, respectively. [9,18]

E. coli is the predominant organism causing UTI in the present study. Maximum susceptibility of *E. coli* isolates was seen to fosfomycin i.e. 98.04%. Colistin wasn't tested as it has been kept as a reserve antibiotic for more severe infections due to its ability to cause severe side effects and is recommended only as a last resort. [19] In another study by Kishore et al. in 2020 (Dehradun, India), the susceptibility of *E. coli* to various antimicrobials seen was fosfomycin at 98.9%, colistin at 100%, aminoglycosides at 97.8%, carbapenems at 89.6%, and nitrofurantoin at 83%, which is similar to the present study. Their study also demonstrated high resistance of *E. coli* to cephalosporins (98.9%), quinolones (91.2%), and co-trimoxazole (90.6 %).

In the study by Sabharwal and Sharma in 2015, the percentage susceptibility of *E. coli* to fosfomycin was 97.2%, nitrofurantoin 94.5%, imipenem 93.5%, cefepime 92.9%, and the least effective was amoxicillin at 23.7%. [16] These results indicate that fosfomycin can be an effective drug for UTI caused by *E.coli*.

Fosfomycin susceptibility to Klebsiella pneumoniae was observed to be 65.75%. Overall, *K. pneumoniae* demonstrated lower susceptibility compared to E. coli (p=0.00000158).

In a study by Kishore et al. in 2020, *K. pneumoniae* was found to be maximally susceptible to colistin (100%). A large percentage of *K. pneumoniae* isolates were also susceptible to fosfomycin (86.7%), carbapenems including imipenem, meropenem, and ertapenem (73.3%), and aminoglycosides (73.3%), although the susceptibility was lower compared to that of *E. coli*. [18] Banerjee et al. in 2017 too reported 64/67 (95.52%) *K. pneumoniae* isolates to be

susceptible to fosfomycin. The percentage susceptibility to various other antimicrobials were colistin (100%), meropenem (68.66%), imipenem (68.66%), and nitrofurantoin (44.78%). Least effective antimicrobials were amoxicillin-clavulanate (17.91%) and cephalosporins (cefazolin at 29.85%,ceftriaxone at 29.85%). Therefore, fosfomycin can be considered as a better drug for *K. pneumoniae*. [17]

Among the other *Enterobacterales* species too, highest susceptibility (92.3%) was seen to fosfomycin. In a study by Sreenivasan et al. in 2019 (Puducherry, India) which evaluated fosfomycin resistance in multidrug-resistant (MDR) *Enterobacterales* (other than *E.coli* and *K. pneumoniae*) fosfomycin susceptibility ranged from 0 to 25%. Sabharwal and Sharma in 2015, have reported over 90% susceptibility for *Proteus mirabilis*.

E. coli has been reported to be the major etiological agent worldwide among ESBL-producing uropathogenic bacteria. [20] A high susceptibility of the ESBL producing *Enterobacterales* (90.62%) to fosfomycin was observed. All ESBL producing strains of *E. coli* and 97.46% of non-ESBL *E. coli* were susceptible. Susceptibility of ESBL and Non-ESBL producing *K.pneumoniae* was lower (66.66% and 65.62%) which is makes it a less effective treatment for *Klebsiella* species than for E coli (p=0.001815). Since there was no ESBL seen in the other *Enterobacterales*, fosfomycin can be used for therapy for these organisms too.

In the present study, MDR *Enterobacterales* demonstrated 83.23% susceptibility to fosfomycin. In studies by Banerjee et al, Pallam et al & Sahni et al, a similar or higher susceptibility has been reported [118/123(95.93%; 264/326(87.3%); 75.7% for *E.coli*]. [17,25,26]

In the present study, 71.62% of CRE isolates and 93.86% of non-CRE isolates demonstrated susceptibility to fosfomycin. The difference was statistically significant (p value-0.00001431). Banerjee et al (2017) have also reported similar susceptibility [41/46 (89.13%) for CRE isolates at 239/242(98.76%) in non-CRE]. This indicates that this drug is more effective in non-CRE than in CRE cases. (p=0.00001431). The study by Kishore et al (2020) also demonstrated good susceptibility to fosfomycin in CRE isolates of all 16 (100%) *E. coli*, 5/8 (62.5%) of *K. pneumoniae*, all four isolates (100%) of *Proteus* species, 2/4 (50%) of *P. aeruginosa*, all five isolates (100%) of *Citrobacter* species and the single isolate of *Acinetobacter* species. Overall, 35/40(87.5%) isolates were susceptible. Since carbapenems have a high efficacy against many bacterial species with lesser adverse reactions, they are being used indiscriminately leading to emergence and rapid spread of resistance to them. [21]

No contraindications exist for the administration of fosfomycin with other medications. In fact, synergistic effect is seen when given as a part of combination therapy (with piperacillin-tazobactam, ceftazidime and minocycline for *Pseudomonas* species, with piperacillin-tazobactam, amikacin, gentamicin, ceftazidime, and colistin for *Acinetobacter* species and with piperacillin-tazobactam, meropenem, ceftazidime, levofloxacin or gentamicin for *Enterobacterales*). [14,22,23] Drugs recommended by Samonis et al in combination with fosfomycin for Enterobacterales are imipenem and meropenem where it was found that among the 50 serine carbapenemase-producing *K. pneumoniae* isoltaes studied, synergy with imipenem and meropenem was 74%and 70% respectively. [22]

The higher fosfomycin susceptibility among isolates recovered from cases in outpatient settings compared to ward patients and ICU‘s is understandable as hospital environment is more prone to have resistant organisms. [24] Saperston et al (California, 2013) have also demonstrated higher resistance to all commonly used antibiotics in the inpatients as compared to outpatients. Pallam et al (2019), who studied antibiotic resistance profile of different isolates in different wards, noted that among E.coli (n=217), no resistance to fosfomycin was seen in 152 isolates from medicine, 52 isolates from urology and seven from nephrology. [25] It appears that the antimicrobial will be more effective in outpatient settings than in inpatients as seen in other earlier studies too. [26, 27,28]

Fosfomycin also demonstrated good susceptibility to *Enterococcus* species. All *E. fecalis* were susceptible and only one isolate of *E. faecium* (1/16, 6.25%) was resistant. The antibiotics with highest in vitro effectiveness against *Enterococcus* species apart from fosfomycin were vancomycin (100%), teicoplanin (100%) and linezolid (100%). But due to the serious side effects associated with these antimicrobials along with the parenteral mode of dosage, fosfomycin can be considered as a first choice. [29]

In a study by Banerjee et al in 2017, 97.72% *Enterococcus* species were found to be susceptible to fosfomycin. [17] Kishore et al in 2020 demonstrated susceptibility to fosfomycin in 16/20 (80%) isolates of *E. faecalis* and in the single isolate of *E. faecium*. [18] In a study by, Sabharwal et al in 2015, all 20 *Enterococcus* species were susceptible to fosfomycin. [16]

Ou and Nadeau in 2017 studied 31 VRE strains isolated from urine specimens, 25/31(80.64%) of these vancomycin resistant *E. faecium* species were susceptible to fosfomycin.[5]

Limitations

A limitation of this study was that it was done to assess only the in-vitro activity of fosfomycin and not clinical outcome in patients.

Conclusions

Fosfomycin was found to have good susceptibility profile in both *Enterobacterales* and Enterococcus species which are the primary urinary tract infection pathogens. Its urinary concentration and safety profile are higher compared to commonly prescribed antimicrobials for MDRE and CRE pathogens and is also recommended in pregnancy. This study demonstrates that fosfomycin has a high potential to emerge as a promising and safe alternative oral agent for both outpatient and inpatient therapy of UTIs, with better patient compliance particularly in resource poor countries like India.

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