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Evaluation of the spectrum of uropathogens, prevalent antimicrobial resistance and prospects of the newbie "fosfomycin"

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Abstract
Introduction: *Urinary tract infections (UTIs) are among the commonest infections impinging morbidity in all age groups. Emergence of antimicrobial resistance is a global problem among the uropathogens, which results in therapeutic failure.*
Objectives: *To investigate the spectrum of uropathogens, their in vitro susceptibility to the commonly used antibiotics and to fosfomycin, and also to determine the prevalence of various antibiotic resistance patterns among the cultured uropathogens.*
Materials and Methods: *The study was conducted prospectively in the department of Microbiology of a tertiary care hospital from April 2017 to July 2017. A total of 1797 non-duplicate urine samples obtained from clinically suspected UTI patients were included in the study and were processed for bacterial culture and antibiotic sensitivity testing (AST). AST and detection of various resistance phenotypes was done as per Clinical Laboratory Standards Institute (CLSI) guidelines.*
Results: *Bacteriological culture of urine samples yielded 406 (93.33%) gram-negative isolates and 61 (17%) gram-positive isolates. The 406 gram-negative isolates represented 388 (95.97%) Enterobacteriaceae isolates, 321 (82.73%) of which were Escherichia coli. Pseudomonas spp. constituted 4.14% of bacterial isolates including 3 metallo beta-lactamase (MBL) producers. Amongst the gram-negative bacteria tested, 153 (34.93%) were extended spectrum beta-lactamase (ESBL) producers. Twenty-seven (6.96%) Enterobacteriaceae isolates were carbapenem resistant Enterobacteriaceae (CRE). Among the Gram positive cocci (GPC) vancomycin, teicoplanin, linezolid and nitrofurantoin were reported highly sensitive. Among the Enterobacteriaceae, colistin (except Proteus spp & Morganella spp.) was 100% sensitive, cefoperazone-sulbactum and piperacillin-tazobactam were sensitive in 89% of isolates approx., while amikacin was 85.57% sensitive. Nitrofurantoin showed 91% (291) sensitivity to E.coli. E.coli and Enterococcus spp. showed 94.39% and 100% susceptibility to fosfomycin respectively. 91.5% (130/142) ESBL- E.coli were sensitive to fosfomycin.*
Conclusion: *E.coli is the most common urinary isolate. Among uropathogens, resistance mechanisms like ESBL production, CRE and other multi drug resistant (MDR) mechanisms are prevalent. Fosfomycin has remarkable sensitivity among E.coli and also in Enterococcus spp. and may be considered an effective oral empirical anti-UTI antibiotic against many superbugs.*

Key words: uropathogen, fosfomycin, ESBL, CRE

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I. Introduction

Urinary tract infections are commonly encountered in day to day clinical practice. UTI is mainly caused by gram negative bacteria (GNB).[1],[2],[3] Indiscriminate and inappropriate use of antibiotics has attributed to the global emergence of multi-drug resistant (MDR) bacterial strains, endangering the efficacy of antibiotics. Hence, continuous evaluation of bacterial pathogens and bacterial sensitivity profiles against the antibiotics is of utmost importance. At the same time, prevalent drug resistance has also prompted evaluation of non-traditional antibiotics that were not used in abundance in the past.[4] Recently one such antibiotic; fosfomycin has been introduced in India and has aroused a ray of hope that it may act as a convenient oral alternative to the current therapeutic agents of UTI.

Fosfomycin-trometamol has a unique chemical structure which is unrelated to any other known antibacterial agent. It is well tolerated orally and has a broad spectrum of activity.[5],[6],[7] A recent study has mentioned its use in intravenous route for treatment of complicated UTI both as monotherapy and in combination therapy with meropenem.[8] Resistance to this drug is usually acquired by chromosomal mutations and do not spread easily.[5] There are only a few Indian studies evaluating the *in vitro* activity of fosfomycin against uropathogens.

With this background, we planned this study to investigate the spectrum of uropathogens, their in vitro susceptibility to fosfomycin and to other antibiotics, and also to determine the prevalence of various antibiotic resistance patterns among the isolated uropathogens. Routinely used phenotypic test methods and maintenance of proper quality standards assured convenience as well as less economic burden while conducting the study in a resource poor laboratory.

II. Materials And Methods

This observational study was conducted from April 2017 to July 2017 in the Microbiology department of a tertiary care hospital of West Bengal, India, in conformity with all ethical guidelines. Total 1797 non-duplicate urine specimens were processed during the study period. Urine samples obtained were mostly freshly voided midstream clean catch. In catheterized patients, urine was aseptically aspirated from catheter after proper catheter clipping. Samples were inoculated on blood agar and MacConkey agar plates using standard calibrated loop following the semi quantitative urine culture technique and significant growth of the potential pathogens was inferred according to the General Interpretative Guidelines for Urine Culture (Bailey &Scott). The significant pathogens were identified by standard biochemical procedures and followed with antibiotic susceptibility testing by Kirby-Bauer disk diffusion (KBDD) method. Results of various Enterobacteriaceae isolates for in vitro response to fosfomycin was interpreted according to CLSI guidelines for *E.coli*.[9] Fosfomycin and colistin e-test strips were used to determine the respective Minimum inhibitory concentration (MIC) values.

Multi-drug Resistant bacteria were defined by resistance to three or more antimicrobial classes. ESBL production was confirmed by disc potentiation test using ceftazidime (30µg) and ceftazidime-clavulunate (30/10µg) combination. Meropenem or ertapenem resistant isolates were tested for MBL production by double disc synergy test using EDTA. Test for Methicillin resistance in *Staphylococcus spp.* (MRS) was performed by using cefoxitin (30µg) disc. High level aminoglycoside resistance (HLAR) in *Enterococcus spp.* was tested using gentamicin (120µg) discs. The data accrued was analyzed using Microsoft-Excel and Vassar-Stat softwares. Qualitative data analysis was done by Chi-square test. Null hypothesis was rejected at $P < 0.05$.

III. Results

Among 1797 urine samples, 412 (22.9%) samples were culture positive with 435 bacterial isolates. 23 samples showed significant growth of two pathogens. Among the symptomatic sample providers, majority were females (n = 1122, 62.44%) and the female to male ratio was 3:1. The age distribution of culture confirmed patients was 6.06% for children (10months – 12years), 50.73% for middle aged patients (>12 years - 60 years) and 43.2% for old aged patients (>60 years - 95 years). The distribution of various bacterial isolates in our study is shown in Figure-1. Sensitivity profile the isolated of uropathogens is shown in Tables-1&2.

Figure 1: Distribution of various bacteria (in numbers) isolated in our study

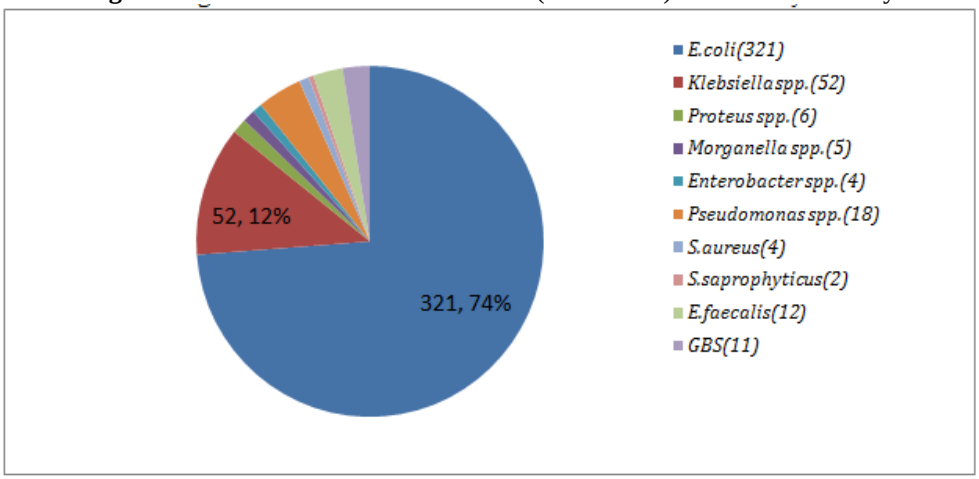


Table1: Sensitivity profile of Gram positive cocci

	S. aureus (4)	*S.saprophyticus* (2)	*Enterococcus spp.* (12)	*Group B Streptococcus: GBS* (11)
Penicillin	0	0	8(66.7%)	11(100%)
Amoxicillin-clav	4(100%)	2(100%)	12(100%)	11(100%)
Cefoxitin	4(100%)	2(100%)	12(100%)	11(100%)
Gentamicin	3(75%)	2(100%)	8(66.7%)	-
Amikacin	3(75%)	2(100%)	-	-
Levofloxacin	0	2(100%)	3(25%)	7(63.6%)
Cotrimoxazole	4(100%)	2(100%)	-	0
Nitrofurantoin	4(100%)	2(100%)	10(83.3%)	11(100%)
Vancomycin	4(100%)	2(100%)	12(100%)	11(100%)
Linezolid	4(100%)	2(100%)	12(100%)	11(100%)
Teicoplanin	4(100%)	2(100%)	12(100%)	11(100%)
Fosfomycin	-	-	12(100%)	-

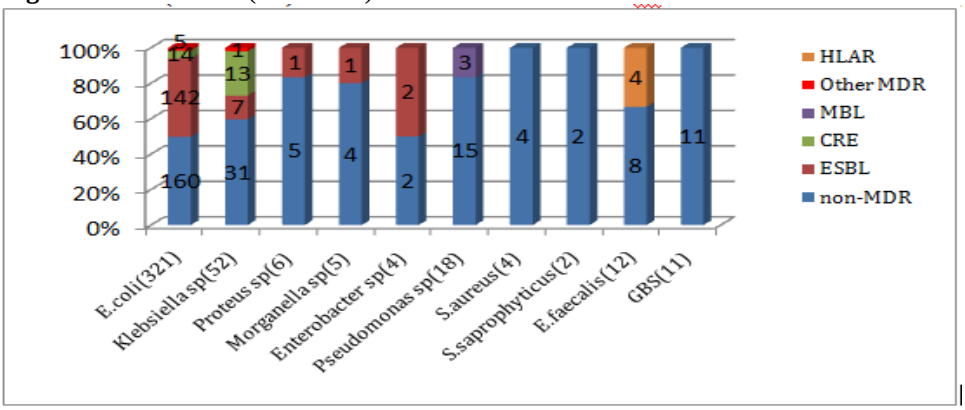
Among the Gram positive cocci (GPC), the highest level of susceptibility was observed for vancomycin, teicoplanin and linezolid (all 100% sensitive) followed by nitrofurantoin to which only two *Enterococcus spp.* isolates were resistant (Table-1). Surprisingly, fluoroquinolones were not effective in vitro in any *S.aureus* isolate. All *Staphylococcus spp.* isolates were sensitive to co-trimoxazole.

Table-2: Sensitivity profile of Gram negative bacilli

	E.coli (321)	*Klebsiella spp.* (52)	*Proteus spp.* (6)	*Morganella spp.* (5)	*Enterobacter spp.* (4)	*Pseudmonas spp.* (18)
Amoxycillin	72(22%)	1(2%)	3(50%)	0	0	9(50%)
Amoxicill-Clav	169(53%)	33(64%)	5(83%)	0	1(25%)	0
Cephalexin	124(39%)	24(46%)	4(67%)	0	0	-
Cefuroxime	141(44%)	27(52%)	4(67%)	0	0	-
Ceftriaxone	158(49%)	31(60%)	5(83%)	4(80%)	3(75%)	0
Ceftazidime	158(49%)	31(60%)	5(83%)	3(60%)	3(75%)	9(50%)
Cefepime	163(51%)	32(62%)	5(83%)	4 (80%)	3(75%)	9(50%)
Cefopera-Sulba	294(92%)	38(73%)	6(100%)	4(80%)	4(100%)	10(56%)
Piperacil-Tazo	296(92%)	38(73%)	6(100%)	4(80%)	4(100%)	11(61%)
Imipenem	307(96%)	41(79%)	6(100%)	4(80%)	4(100%)	14(78%)
Meropenem	307(96%)	41(79%)	6(100%)	4(80%)	4(100%)	13(72%)
Ertapenem	306(96%)	39(79%)	6(100%)	4(80%)	4(100%)	-
Amikacin	283(88%)	38(73%)	5(83%)	3(60%)	3(75%)	6(33%)
Gentamicin	194(16%)	31(60%)	5(83%)	2(40%)	2(50%)	6(33%)
Nalidixic Acid	54(17%)	24(46%)	2(33%)	0	1(25%)	-
Norfloxacin	99(31%)	28(54%)	4(67%)	1(20%)	2(50%)	5(28%)
Levofloxacin	105(33%)	31(60%)	4(67%)	1(20%)	2(50%)	5(28%)
Cotrimoxazole	19360(%)	26(50%)	3(50%)	1(20%)	2(50%)	0
Nitrofurantoin	291(91%)	12(23%)	1(17%)	0	2(50%)	4(22%)
Fosfomycin	303(94%)	49(94%)	6(100%)	3(60%)	1(25%)	-
Colistin	321(100%)	52(100%)	-	-	-	18(100%)

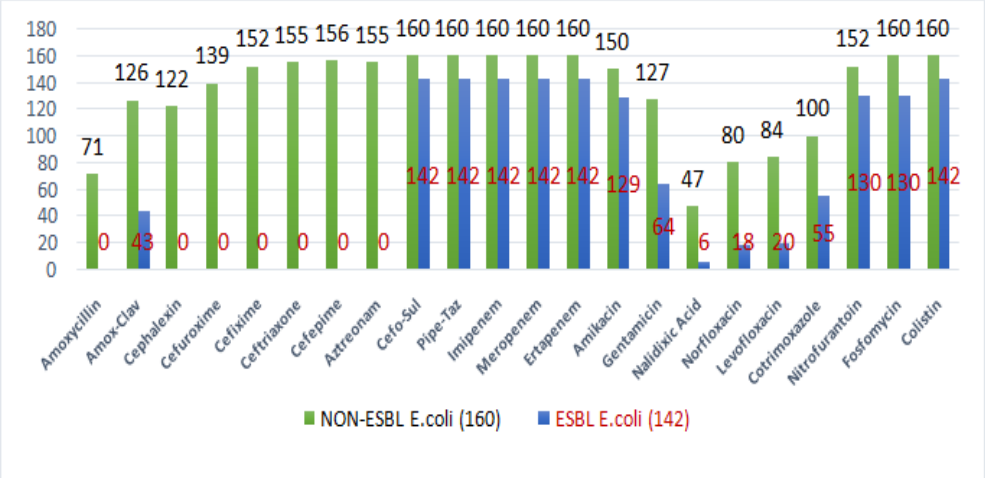
Among the Enterobacteriaceae, amikacin was sensitive in 85.57% isolates while cefoperazone-sulbactum and piperacillin-tazobactam were sensitive in 89% of isolates approx. 60.12%, 60.31% and 36.86% isolates were sensitive to co-trimoxaole, gentamicin and ofloxacin, respectively. Nitrofurantoin showed good in vitro sensitivity to *E.coli* 91% (291). Upto 93.29% (362) of Enterobacteriaceae and 72.22% (13) of non-fermenters were reported sensitive to meropenem in our study. 100% tested GNB were sensitive to colistin by E-test method. *Pseudomonas spp.* was well sensitive to carbapenems except for 3 MBL producers, though all MBL producers were sensitive to colistin. Overviewing AST results of oral antibiotic panel to *Pseudomonas spp.* isolates, 5 isolates were sensitive to norfloxacin and 5 sensitive to nitrofurantoin. 362 (93.3%) Enterobacteriaceae isolates were tested susceptible to fosfomycin. The respective MDR patterns among various bacterial isolates are shown in Figure-2.

Figure 2: Distribution (in number) of non-MDR bacterial strains vs various MDR strains



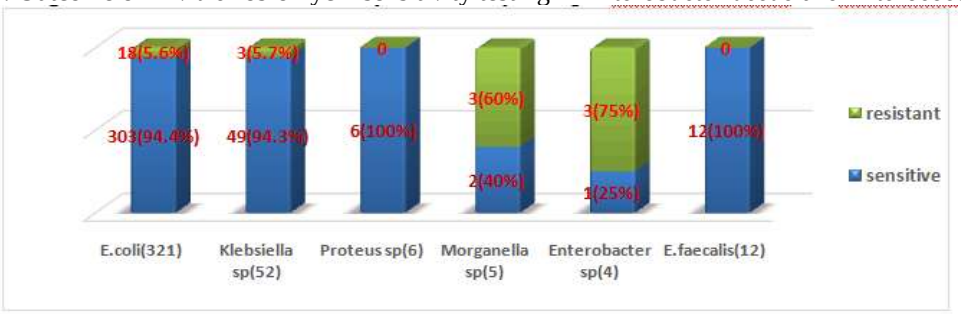
The most common resistance pattern identified phenotypically was ESBL production followed by CRE. No, MBL producers were detected among the Enterobacteriaceae, but 3 out of 18 (16.67%) *Pseudomonas* isolates were MBL producers. Among Enterobacteriaceae, only 13 (8.49%) ESBL producers & 8 (29.33%) CRE were resistant to fosfomycin. Carbapenem resistant isolates (CRE & MBL) were resistant to all tested antibiotics except colistin, amikacin and at times gentamicin.

Figure 3: Comparison of AST results (number of sensitive isolates) of ESBL *E.coli* vs non-MDR *E.coli*



The ESBL producing *E.coli* isolates showed significantly higher resistance ($P < 0.001$) to the tested antibiotics *viz.* amoxycillin-clavulunate, levofloxacin, co-trimoxazole, nalidixic acid and gentamicin than the non-MDR isolates (Figure-3). Simultaneously, cfoperazone-sulbactum, piperacillin-tazobactum, carbapenems, amikacin, nitrofurantoin, fosfomycin and colistin showed no significant difference of sensitivity ($P > 0.05$) in ESBL vs non-MDR E.coli isolates. In vitro response of various *Enterobacteriaceae* and *Enterococcus spp.* isolates to fosfomycin is shown in Figure-4.

Figure 4: Outcome of *in vitro* fosfomycin sensitivity testing in *Enterobacteriaceae* and *Enterococcus spp*.



Fosfomycin showed good susceptibility against both ESBL-producing and non-MDR *E. coli* isolates (Figure-3). *E.coli* showed the overall highest susceptibility rate of 94.4% to fosfomycin (Table-2). High sensitivity to fosfomycin was also seen in our study in *Klebsiella spp.* isolates, though, the response of *Enterobacter spp.* and *Morganella spp.* isolates were not satisfactory in this context. Fosfomycin was highly sensitive (100%) in *Enterococcus spp.* isolates (Figure-3). On testing by KBDD, one *E.coli* and two *Klebsiella spp.* isolates showed hetero-resistance and both these strains were resistant to fosfomycin (MIC≥256µg/ml) by e-test method following MIC interpretative criteria (CLSI) for *E.coli*.

IV. Discussion

This study was conducted to assess the spectrum of uropathogens, and their response to the currently deployed antimicrobials with emphasis on the recently introduced antibiotic fosfomycin. Out of 412 (22.9%) culture positive samples, 23 samples belonging to catheterized patients showed dual significant growth of potential uropathogens. The presence of more than one potential uropathogens in midstream urine at colony counts >100,000 CFU/ml is consistent with a polymicrobial etiology of UTI. Polymicrobial infections occur most often among the elderly, immunocompromised, and those with indwelling catheters, HIV, malignancy, and diabetes.[10] Female predominance was observed among the studied patients as shown in previous studies.[1,4,11] We noted that UTI prevailed maximally in middle age group, and high prevalence was also noted in old age group similar to findings of Yeganeh-Sefidan F *et al*.[11]

In our study, among the 24.2% culture confirmed UTI, there was huge predominance of GNB (93.33%) similar to previous studies.[10,12] We found that majority 388/435 (89.2%) of uropathogens were *Enterobacteriaceae* predominated by *E.coli* as shown by several previous researches.[1],[4],[11],[12] *Klebsiella spp.* was the second most common isolate, though the prevalence was quite low (11.9%) as compared to *E.coli* (73.8%) as previously documented by Sultan A et al and Sabarwal R et al.[1,4]. Among the 29/435 (6.7%) GPC isolates, most common was *E.faecalis* (41.4%), followed by GBS (37.9%). 5-25% of uncomplicated UTI is reportedly caused by Gram positive bacteria like Staphylococcus saprophyticus, Enterococcus faecalis, GBS and other less frequently isolated organisms.[10,12]

Multi drug resistance is a frequent nuisance among uropathogens and we observed large fraction of ESBL producers among the GNB, concordant with findings of previous researchers.[1],[3],[11],[13],[14] Furthermore, we also observed occurrence of 27 (6.96%) CRE and also few MBL producing *Pseudomonas spp.* isolates as supported by Eshetie S et al and Begum N et al.[15,16] Highest carbapenem resistance was noted in *Klebsiella spp.* ESBL producing E.coli were highly resistant to many antibiotics confirming the previous reports.[11] Colistin showed (100% sensitive by e-testing) similar to previous reports.[15,16] In contrast to findings by previous researchers, we did not find any MRS, which may be due to lower prevalence of *Staphylococcus spp.* isolates in our study. Also, the prevalence of HLAR among *Enterococcus faecalis* was 33.34% in our study, lower occurrence compared to that reported by Sultan et al.[1] In ambulatory patients, oral antibiotics are preferred which include limited options like amoxicillin-clavulunate, oral cephalosporins, fluoroquinolones, co-rimoxaoleand nitrofurantoin. In this oral antibiotic panel; all except fluoroqinolones and co-trimoxaole showed good response in non-MDR *E.coli* isolates. However, it is worth emphasizing that approx. 50% *E.coli* isolates in our study were MDR strains (ESBL/CRE/other undetermined MDR mechanisms) and were highly resistant to all commonly used oral antibiotics except nitrofurantoin, as previously reported by Garau M et al.[17] Interestingly, in our study nitrofurantoin showed remarkable susceptibility against both non-MDR and MDR phenotypes of uropathogenic bacteria (except *Klebsiella spp.*) and was closely overshadowed only by fosfomycin. Our finding of *E.coli* showing 94.4% susceptibility to fosfomycin is in coherence with past literature which mentions susceptibility of *E.coli* to fosfomycin ranges from 88% to 100%.[4,11,12,18,19] Susceptibility of *Klebsiella spp.* to fosfomycin (94.23%) was almost similar to that of *E.coli*. However, previous literature documented poor uptake of this drug by *Klebsiella*[5]. This contradiction might be due to our low sample size (52) of *Klebsiella isolates*. While *Proteus spp.* was 100% sensitive, *Morganella spp.* was cent percent resistant to fosfomycin as supported by Demir T et al.[20] We found that among *Enterobacteriaceae*, only 13 (8.49%) of ESBL-producers and as high as 8 (29.33%) CRE were resistant to fosfomycin. According to Sahni RD et al 81% of ESBL producing *E.coli* were susceptible to fosfomycin, while 75.7% of other MDR *E.coli* were found to be susceptible to fosfomycin and almost similar to our finding, previously 99% of *Enterococcus* spp were shown to be sensitive. [19]

Our population being fosfomycin naive, showed promising *in vitro* activity against most MDR urinary pathogens. It may be considered a good candidate for empirical antibiotic therapy in UTI against *E.coli* and also *Enterococcus spp*., the commonest GNB and GPC respectively isolated in our study. However, hetero-resistance seen on AST by KBDD method may be concerning and this further emphasizes need of monitoring the treatment. Studies are needed regarding clinical follow up and therapeutic success and prevalence of hetero-

resistance. Practically fosfomycin may be an answer to most superbugs but definitely not blindly applicable for all of them; especially carbapenem resistant Enterobacteriaceae.

V. Conclusion

Fosfomycin and colistin are quite old drugs; however, these have been re-introduced in India very recently. Our study along with many others demonstrated that fosfomycin can be used as an initial empiric therapeutic option in the management of UTI. Colistin; being a systemic drug with very high in vitro sensitivity, must be used as a reserve drug in CRE infections where all other antimicrobials are literally ineffective. Random and unmonitored use along with inappropriate dosage and over the counter availability may prove counterproductive. It should be kept in the mind that faulty use tends to enthrust selection pressure favoring the emergence of resistant strains. Otherwise, these wonder drugs might lose their antimicrobial efficacy and mankind will be devoid of important weapons against the superbugs.

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