ORIGINAL ARTICLE

Fosfomycin: A Substitute in Therapeutic Options for Extended Spectrum Beta-lactamase Producing Uropathogens

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ABSTRACT

Background: The emergence of antibiotic resistance among pathogens causing urinary tract infections (UTI) has made treatment options limited. The use of fosfomycin along with other drug combination can significantly address this problem. Our study aimed to identify the rate of resistance among uropathogens and their susceptibility patterns to fosfomycin along with other antibacterial agents.

Methods: The retrospective study was conducted at Jinnah Sindh Medical University in collaboration with Dr. Tahir Laboratory, Karachi. A total of 146 urine samples were included which were processed for antibacterial susceptibility testing by Kirby-Bauer disk diffusion method and rate of resistance for antibacterial agents especially fosfomycin were recorded. The statistical analysis was performed by using Chi squared tests and $p>0.05$ was considered statistically significant.

Results: The study reported lowest rate of resistance for fosfomycin among *Escherichia coli* 3(5.3%), *Klebsiella pneumoniae* 7(14%) and *Pseudomonas aeruginosa* 9(22.5%) in comparison with ampicillin, which showed resistance in 43(76.8%), 41(82%) and 39(97.5%) cases of *E. coli*, *K. pneumoniae* and *P. aeruginosa* respectively. The subgroup carbapenem resistant *Enterobacteriaceae* (CRE) and extended spectrum β-lactamases (ESBLs) producers were seen noticeably high in *P. aeruginosa*. Overall, the female to male ratio was 1.4:1 (87/59), showing female preponderance ($p=0.02$). A majority of patients belonged to adult age group (61.6%) followed by senior adults (23.2%, $p=0.05$).

Conclusion: High levels of resistance to commonly used antibiotics were observed. The increasing rate of resistance among *Enterobacteriaceae* to cephalosporin and ampicillin is an alarming situation. In this context, fosfomycin is an interesting alternative option in treatment of complicated and uncomplicated urinary tract infections.

Keywords: Antibiotic Resistance; *Enterobacteriaceae*; Extended Spectrum Beta Lactamase; Fosfomycin; Urinary Tract Infection.

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INTRODUCTION

The antibacterial resistance has become an exasperating yet challenging issue globally. The irrational use of antibiotics in the field of human and veterinary medicine, agriculture and farming has brought the epoch of antibacterial drugs, nearly to an edge. The antibiotic resistance has shown an

increment of 9% from 2014 to 2017 in United Kindom[1]. In United State of America, the multidrug resistant uropathogens have been reported in 7% to 13% cases in last decade[2]. The condition in Asian countries is even more serious, the prevalence of resistant uropathogens is reported as 38.3% by SMART (Study for Monitoring Antimicrobial Resistance Trends) program[2]. The bacterial resistance has become an alarming sign in urological practices in general, and urinary tract associated infections in particular. The extended spectrum beta lactamase (ESBL) producing *Enterobacteriaceae* in context to uropathogens have become a complex issue when treatment modalities are concerned.

The ESBL bacteria exhibit resistance towards third generation cephalosporins, penicillins and monobactams. The ESBL *E. coli*, *K. pneumonia*, *Pseudomonas* species, *Proteus* species and other uropathogens have shown decreased activity against cephalosporins, quinolones, and aminoglycosides and even with cephamycins[3]. Trimethoprim-sulfamethoxazole has also become ineffective in ESBL pathogens and treatment of urinary tract infections by a single potent drug is becoming difficult day by day. The scenario is more complicated with hospital associated urinary tract infections where resistant strains of *Pseudomonas* and *Acinetobacter baumannii* are found to be involved. Therefore, the advent and practice of newer antibacterial drugs is current era's most pivotal requirement.

Fosfomycin- promethazine is a synthetic, broad spectrum, bactericidal antibiotic that works by inhibiting pyruvyl-transferase during bacterial cell wall synthesis, and it decreases bacterial adherence to epithelial cells in the urinary tract. Fosfomycin is considered as first line of therapy for uncomplicated UTI[4]. Fosfomycin has shown efficacy in both *in vitro* and *in vivo* studies for treating UTIs caused by ESBL-producing *Enterobacteriaceae* and vancomycin resistant enterococci[5]. In addition, it is an alternative option for multidrug resistant (MDR) organisms, allergies where the intravenous antibiotics cannot be recommended[6]. The recent studies have reported its activity against methicillin resistant *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*[7].

In developing countries like Pakistan, where health care facilities are inadequate, the emergence of resistant bacterial strains is no lesser than havoc. Data from Pakistan regarding susceptibility patterns towards fosfomycin is limited and newer studies are required in order to get awareness of current scenario in Pakistan. Therefore, this study was designed to get insight of fosfomycin susceptibility patterns among local population.

METHODS

This retrospective study was conducted at Jinnah Sindh Medical University after getting ethical approval from Institutional Review Board (JSMU/IRB/2019/274) and Dr. Tahir laboratory, Hamdard University and hospital. A total of 146 urine samples which showed positive bacterial isolates collected between the time periods of July 2019 to July 2020, were included in the study. The samples were collected and processed in Dr. Tahir Laboratory. The data regarding patient's age, gender and registration number and isolated uropathogens belonging to *Enterobacteriaceae* were recorded. The cases with incomplete data were excluded from study.

The urine samples were collected in sterile screw capped containers and was properly labeled. The samples were inoculated on Blood, MacConkey's and cysteine lactose electrolyte deficient (CLED) agar. The identification of bacterial isolates was made by appropriate biochemical tests and was categorized as extended spectrum beta lactamases (ESBLs) and carbapenem resistant *Enterobacteriaceae* (CRE) based on sensitivity guidelines provided by Clinical Laboratory Standard Institute (CLSI, United States of America, 2020). The organisms which showed resistance towards third generation cephalosporins (ceftazidime, ceftriaxone and cefixime), monobactams (aztreonam) and were inhibited by β Lactamase inhibitors (clavulanate, sulbactam and tazobactam) were termed as ESBLs[8]. On the other hand, the *Enterobacteriaceae*, which mediated resistance towards carbapenems (ertapenem, meropenem and imipenem), were termed as CREs[9].

The antibacterial susceptibility testing (AST) was performed by Kirby-Bauer's disc diffusion method on Muller-Hinton agar. The zone of inhibition around antibiotic discs was measured and organisms were considered sensitive, intermediate or resistance according to the cut off values provided by CLSI guidelines 2020. The antibiotic discs were purchased from Oxoid (United Kingdom). Following antibiotic discs were used in AST: amoxicillin- clavulanic acid (20/10µg), ampicillin (10µg), cefotaxime (30µg), ceftazidime (30µg), cefepime (30µg), cefuroxime (30µg), aztreonam (30µg), gentamicin (10µg), amikacin (30µg), ciprofloxacin (5µg), nalidixic acid (30µg), trimethoprim-sulfamethoxazole (30µg), nitrofurantoin (300µg) and fosfomycin (200µg).

The screening test for ESBL was performed by the method proposed by CLSI [10]. *E. coli* ATCC 25922 was used as quality control strains. The bacterial isolates were supposed to be ESBL, when the zone of inhibition for ceftazidime was ≤22mm and for cefotaxime was ≤ 27mm respectively. The double disc synergy test was used to confirm ESBL producers. In this test, amoxicillin-clavulanic acid (20/10µg) was placed on

Muller-Hinton agar plate, which was already streaked with testing organism. The discs for ceftazidime (30µg) and cefotaxime (30µg) were placed about 20mm apart from amoxicillin-clavulanic acid discs. Those phenotypes, which showed phenomenon of synergism, were confirmed as ESBL producers.

The CREs were detected by performing sensitivity testing of imipenem, ertapenem and meropenem on Muller-Hinton agar by Kirby Bauer disc diffusion method. The break point for imipenem was ≤19mm while for ertapenem and meropenem was taken ≤ 21mm (proposed by CLSI) [10]. The data were recorded in Statistical Package for Social Sciences (SPSS, IBM USA, version 22). The descriptive statistics and chi square tests were used to analyze the data. The data was presented in the form of tables, graphs and figures.

RESULTS

The study included 146 bacterial isolates of *E. coli, K. pneumoniae* and *P. aeruginosa* belonging to *Enterobacteriaceae*. There were 56 (38.3%) *E. coli* strains, 50 (34.2%) *K. pneumoniae* isolates while in 40 (27.3%) cases, *P. aeruginosa* was recovered. Overall, the female to male ratio was 1.4:1 (87/59), showing female preponderance (p=0.02) as shown in Table 1. A majority of patients belonged to adult age group (61.6%) followed by senior adults (23.2%, p=0.05).The *E. coli* was also most commonly observed in patients falling in adult age group (73.2%), followed by geriatric group (14.3%). The female to male ratio for positivity towards *E. coli* was 1:0.75 (24/32). The *K. pneumoniae* was prevalent in adult age group (58%) and being least common in adolescents (2%). The female to male ratio for UTI caused by *K. pneumoniae* was found to be 1:0.6(30/20). The *P. aeruginosa* also showed the same trend for being commonly observed in adults (73.2%) and least prevalent among children (5.4%). The female to male ratio for *K. pneumoniae* was 1.6:1 (25/15).

Table 1: Demographic characteristics of the study population.

Bacterial Isolates	Gender			Age group				Total
	Male (n)	Female (n)	F:M Ratio	Children (0-10 years)	Adolescents (11-19 years)	Adults (20-59 years)	Senior adults (60 and above)	
Escherichia coli	24	32	1:0.75	3	4	41	8	56
Klebsiella pneumoniae	20	30	1:0.6	5	1	29	15	50
Pseudomonas aeruginosa	15	25	1.6:1	2	7	20	11	40
Total	59	87	1.4:1	10	12	90	34	146
***p*-Value**	**0.02**			**0.05**			**0.05**	

The rate of resistance for various antimicrobial agents among *Enterobacteriaceae* is shown in Table 2. The *E. coli* strains were highly resistant to penicillin group (76.8%) followed by cephalosporins (cefaclor 48.2%, ceftriaxone 41.1% and ceftazidime 37.5%). The *E. coli* isolates were found to be least resistant for fosfomycin (5.3%). About 10.8% samples of *E. coli* were CRE and 41.78% were ESBL producers.

Table 2: Resistance of uropathogens to various antibacterial agents.

Antibiotic Class	Antibacterial* Agent	*Escherichia coli* n (%)	*Klebsiella pneumoniae* n (%)	*Pseudomonas aeruginosa* n (%)
Fosfomycin	FOS	3(5.3)	7(14)	9(22.5)
B-lactamase inhibitors	AMC	13(23.2)	38(76)	29(72.5)
Penicillins	AMP	43(76.8)	41(82)	39(97.5)
Cephalosporins	CFM	20(35.7)	28(56)	23(57.5)
	CRO	23(41.1)	29(58)	19(47.5)
	CEC	27(48.2)	22(44)	22(55)
	CAZ	21(37.5)	21(42)	25(62.5)
	CTX	26(46.4)	26(52)	25(62.5)
Folate pathway inhibitor	SXT	20(35.7)	20(40)	27(67.5)
Monobactams	ATM	15(26.8)	24(48)	21(52.5)
Quinolones	CIP	15(26.8)	23(46)	16(40)
Aminoglycosides	AK	4(7.2)	9(18)	13(32.5)
	CN	14(25)	11(22)	16(40)
Nitrofurantoin	F	11(19.6)	13(26)	11(27.5)
Carbapenem	MEM	6(10.8)	3(26)	16(40)

Abbreviations FOS=fosfomycin, AMC=ampicillin-clavulanate, AMP=ampicillin, CFM=cefixime CRO=ceftriaxone, CEC=cefaclor CAZ=ceftazidime, CTX=cefotaxime TS=trimethoprim-sulfamethoxazole, ATM=aztreonam, CIP=ciprofloxacin, AK=amikacin, CN=gentamicin, F=nitrofurantoin, MEM=meropenem*

The UTI was found to be more common among females, however relationship between gender and resistance for antimicrobial agents was not established ($p>0.05$). Similarly, there was no association found between age groups and drug resistance ($p>0.05$).

The *K. pneumoniae* showed highest rate of resistance for penicillins (76%). The *K. pneumoniae* isolates were found to be considerably resistant for quinolone group (46%). The rate of resistance was also high among cephems (ceftriaxone 58.2%, cefaclor 44%, and ceftazidime 42%). The fosfomycin came up as the most potent agent against *K. pneumoniae*, being 14% resistant in all cases. The frequency of ESBL producers was 50.44, while 26% isolates were CRE (Figure 1).

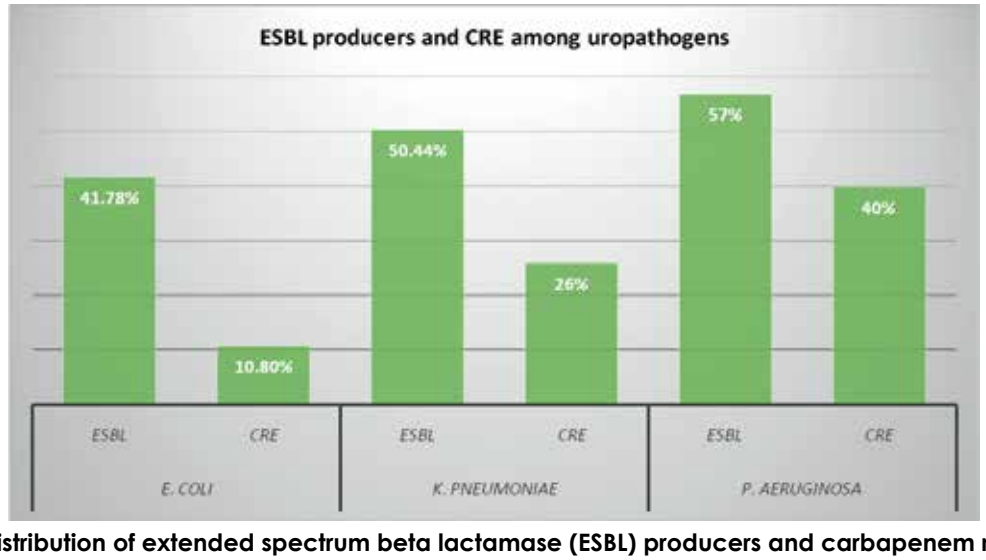

Figure 1: Distribution of extended spectrum beta lactamase (ESBL) producers and carbapenem resistant Enterobacteriaceae (CRE) among uropathogens.

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The rate of resistance in *P. aeruginosa* for penicillin group was significantly high (97.5%) which was followed by folate pathway inhibitors (67.5%).The resistance for cephalosporins was also substantially high (ceftazidime 62.5%, cefaclor 55%, ceftriaxone 47.5%). The 57% *P. aeruginosa* isolates were ESBL producers while 40% fall in CRE group. The resistance towards fosfomycin was observed as 22.5% being highest among all three pathogens (Figure 2).

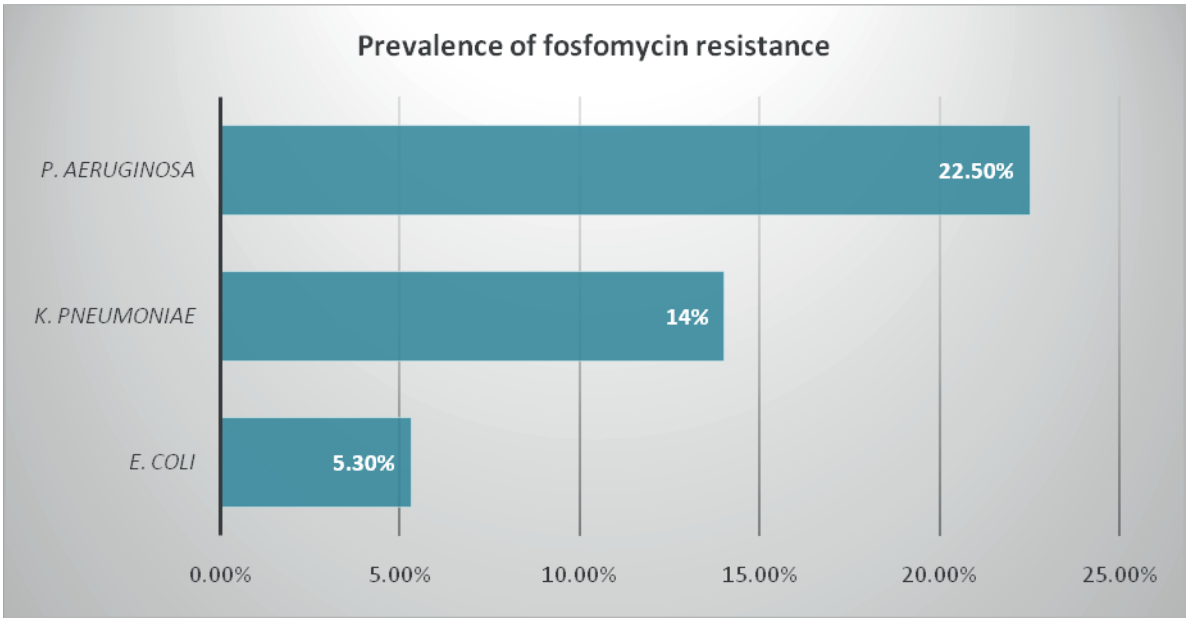

Figure 2: Prevalence of fosfomycin resistance among *Enterobacteriaceae*

DISCUSSION

The current study was conducted to evaluate the antibiotic susceptibility patterns of uropathogens belonging to *Enterobacteriaceae* for fosfomycin in particular. Urinary tract infection (UTI) is one of the commonest infectious diseases, affecting outpatients as well as hospitalized individuals. It is estimated that the lifetime incidence of uncomplicated UTI among adult and sexually active women is about 50-60% [11]. This incidence increases by 20% with increasing age in females[12]. Our study also demonstrated the increased frequency of UTI in female population in comparison with males. Similar results have been reported by Mohammed et al. and Sewify et al [13,14]. The females are more prone to contract UTI because of several factors including short urethra, sexual activity, compromised hygienic practices and low levels of estrogen after menopause[15]. According to our study, the age group, which affected most, was adult group i.e. between 20-59 years of age. Our results were in complete agreement with Tan and Chlebicki and Kabugo et al[16,17]. The reasons behind increased prevalence among adults are dependent upon sexual behaviors, use of contraceptive devices, pregnancy, urethral strictures and renal stones[18].

Gram-negative *Enterobacteriaceae*, being positive in 75% to 95% cases, carries the major UTI burden[18]. The increasing rate of resistance among uropathogens has become an agonizing problem globally, which has not savaged even developed world. Pakistan is experiencing the similar serious threat of antimicrobial resistance. The present study showed the rising frequency of extended spectrum beta lactamases (ESBL) producers and carbapenem resistant *Enterobacteriaceae* (CRE). The most common isolated pathogens in our study were *E. coli* (38.3%) followed by *K. pneumoniae* (34.2%) and *P. aeruginosa* (27.3%). These results were in accordance with Yeganeh-Sefidan et al. and Qamar et al. who also documented the same results[19,20]. The penicillin group was found to be least active against aforementioned uropathogens *in vitro* susceptibility testing. The *P. aeruginosa* showed highest rate of resistance (97.5%) towards ampicillin, which was followed by *E. coli* (76.8%) and *K. pneumoniae* (76%). Yeganeh-Sefidan et al., Yekani et al. and Lake et al. also reported the highest resistance of uropathogens towards ampicillin[19,21,22].

The resistance to ciprofloxacin, trimethoprim-sulfamethoxazole and gentamicin was also noteworthy. The *K. pneumoniae* isolates showed highest rate of resistance (44%) to ciprofloxacin in comparison with *P. aeruginosa* and *E. coli,* which showed 40%, and 26.8% resistance respectively. Reports by Reis et al. reinforced the results in present study, indicating increasing resistance to ciprofloaxcin[23]. The results by Qiao et al. are however

contradictory to our results who stipulated higher sensitivity rates of uropathogens to ciprofloxacin[24]. The resistance to ciprofloxacin is conferred by single gene mutation and colonization by ciprofloxacin resistant *Enterobacteriaceae* causes the treatment burden and eventually killing of ciprofloxacin susceptible starins[25]. The ciprofloxacin is one of the most commonly prescribed antibiotics for uncomplicated UTI in Pakistan; rising incidence of resistance is indeed an alarming sign.

The resistance to trimethoprim-sulfamethoxazole (co-trimoxazole) among uropathogens was also significant. The *Pseudomonas* were highly resistant (67.5%) to the co-trimoxazole, our results showed complete agreement with Yekani et al[21]. The aminoglycosides are also prescribed for UTI and cystitis and according to our results; highest rate of resistance to gentamicin was seen in *P. aeruginosa* followed by *E. coli* (25%) and *Klebsiella* (22%). Gajdács and Urbán also documented the increasing resistances for aminoglycosides[26]. On contrary, the amikacin was found to be highly sensitive drug for all uropathogens. The frequencies of resistance by *E. coli, K. pneumoniae* and *P. aeruginosa* were found to be 6.2%, 10.8% and 9.7% respectively.

The third generation cephalosporins are used worldwide to treat complicated and hospital associated infections. This leads to emergence of third generation resistant *Enterobacteriaceae* (3GCREB) particularly among ESBL producers[27]. Often the ESBL production is co related with resistance to trimethoprim-sulfamethoxazole, aminoglycosides and quinolones as the same plasmids encodes resistance genes, which are responsible for ESBL production[19]. In the present study, the prevalence of ESBLs in *E. coli* was as high as 38.4%, While in *K. pneumoniae* and *P. aeruginosa*; it was found to be 56% and 47.5% respectively. Our results are in line with Rizzo et al. who reported the resistance by *E. coli* to 3rd generation cephalosporins as 33.9% and 26.9% respectively[27]. According to current study, the frequency of ESBL production among *K. pneumoniae* was 56% and in *P. aeruginosa* was 47.5%, which clearly reflects the higher incidence of ESBL producers among *Enterobacteriaceae*. The carbapenem resistant *Enterobacteriaceae* (CREs) are related significantly with morbidity and mortality. The prevalence of CRE in the present study was found to be noticeable among uropathogens.

The present study clearly demonstrates the highest rate of sensitivity of all three isolated bacterial species to fosfomycin. According to our results, overall rate of resistance among all isolates to fosfomycin was low. The *P. aeruginosa* showed higher rates of resistance to fosfomycin as compare to *E. coli* and *Klebsiella* species. The reason for low level of resistance among *E. coli* to fosfomycin is usually that fosfomycin is not prescribed for uncomplicated UTI. These stipulated results were in accordance with Yeganeh-Sefidan et al. conversely Huang et al. presented higher rates of resistance among *Enterobacteriaceae* to fosfomycin [19,28]. According to Cao et al., the rate of resistance among *E. coli* isolates was as low as 4.6%, which is comparable to the current study results[29]. The rate of resistance by *K. pneumoniae* in our study was found to be 6.7% so; similar results were documented by van den Bijllaardt et al[30].

CONCLUSION

The present study highlighted the effectiveness of fosfomycin in urinary tract infections especially by *E. coli, K. pneumoniae* and *P. aeruginosa.* The findings suggest the prompt and regular vigilance of antimicrobial resistance among uropathogens so that emergence of resistance by bugs can be controlled.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

Institutional Review Board (IRB) of Jinnah Sindh Medical University approved the study with reference number: JSMU/IRB/2019/274.

PATIENT CONSENT

Consents were taken from all the patients selected in study.

AUTHOR'S CONTRIBUTION

SMH contributed in data collection, manuscript writing and review, FZ conceived the idea, did manuscript writing and data analysis, AS did data entry, contributed in manuscript writing and data analysis, SMH contributed in data collection, data analysis and review, and MH helped in data collection and data entry.

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