MULTI-DRUG RESISTANT ESCHERICHIA COLI AND THEIR SENSITIVITY TO ORAL FOSFOMYCIN IN URINARY TRACT INFECTIONS: A SINGLE-CENTER EXPERIENCE

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ABSTRACT

Objectives: To determine the frequency of Escherichia coli (E. Coli) with multi-drug resistance and sensitivity to oral Fosfomycin in urinary tract infections in a public sector hospital of Peshawar Pakistan.

Material and Methods: A descriptive cross-sectional study with a convenient consecutive sampling technique at the Department of Medicine Khyber Teaching Hospital Peshawar. A total of 179 patients were recruited in the current study. Detailed history and examination were carried out followed by routine baseline investigations. Under rigorous aseptic settings, two clean midstream urine samples from patients exhibiting symptoms of a urinary tract infection were collected. These samples were then promptly transferred to the hospital laboratory for routine evaluation and E.Coli inoculation on culture media. Once E.Coli was detected, it was tested for antibiotic sensitivity and resistance against the antibiotics mentioned. The multi-drug resistant (MDR) strains were isolated and their sensitivity was checked against oral fosfomycin. All the variables of data were recorded in SPSS version 20. Descriptive and inferential statistics will be utilized to elaborate study findings.

Results: The mean age in this study was 37 years with a standard deviation was ±11.27. Seventy-three (41%) patients were males and 106 (59%) patients were females. One hundred and eleven (62%) patients had multidrug-resistant E.Coli among which oral Fosfomycin was sensitive in 108(97%) patients and was resistant in 3(3%) patients presenting with urinary tract infection.

Conclusion: The multidrug-resistant E. coli strains are common in our setup. However, oral fosfomycin has documented sensitivity against these MDR strains of E. coli in the majority of UTI cases.

Keywords: Multidrug-resistant Escherichia coli, Drug Sensitivity, Fosfomycin, Urinary tract infection

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INTRODUCTION

Infections of the urinary tract account for a few of the foremost common microorganism infections worldwide[1]. Females are affected more as compared to males[2]. Presentation of UTI ranges from cystitis, pyelonephritis, and urosepsis. Different microorganisms cause infections of the urinary tract. Escherichia Coli, Enterococcus faecalis, Klebsiella, Pseudomonas, staphylococcus aureus, and proteus are the foremost common uropathogens. E. Coli is one of them, and it accounts for the majority of urinary tract infections (85% in the community and 50% in hospitals)[3]. With time and the environment, the bacteria's resistance pattern changes. There are various resistance mechanisms, such as horizontal gene transfer and recombination of extrinsic DNA and genetic material modification[4]. Antibiotic resistance has grown significantly during the past few years against frequently used antibiotics[5]. Antibiotic resistance has been caused by innumerable factors like overuse and abuse of antibiotics[6]. The augmented trend of antibiotics for treatment has an impact on the bacteria's pattern of resistance. Emerging multi-drug resistant (MDR) E. coli strains make it inappropriate to use many antibiotics, including penicillin, cephalosporin, trimethoprim, quinolones, and gentamycin[7]. This has become a major problem even for uncomplicated UTIs where clearing the infection and lowering morbidity and mortality has become significantly more challenging as a result of the development of this resistance to routinely used antibiotics[8]. Research carried out at the Khyber Teaching Hospital Peshawar, E.Coli was the most frequent bacterial agent, occurring 77.9% of the time. Amikacin sensitivity was 93%. While a different study from the USA concluded that levofloxacin was equally effective for treating urinary

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tract infections as ciprofloxacin[9]. In a different study, 65% of E. coli isolates had multidrug resistance.

Antibiotics are the cornerstone of treatment for urinary tract infections[10]. It is crucial to know how common multidrug-resistant E. coli strains are as well as how susceptible they are to antibiotics. By blocking the enzyme phosphoenol pyruvate synthetase, a bactericidal drug known as fosfomycin blocks the first stage in the synthesis of the cell wall in both Gram-positive and -negative bacteria[11]. A functioning L-a glycerophosphate transport system (GlpT) and the hexose-phosphate absorption system are the two separate transport mechanism systems that allow fosfomycin to enter the cells of bacteria that are fosfomycin-sensitive (UhpT). By preventing the production of N-acetylmuramic acid, it also prevents the creation of peptidoglycan. When used against both Gram-positive and Gram-negative bacteria, fosfomycin displays a broad range of activity. It may work better when used with antibiotics like fluoroquinolones and aminoglycosides. Eighty-nine percent of the bacteria were found to be responsive to fosfomycin, according to a study by Souza RB et al[12]. In pregnant women with a urinary tract infection, the majority of multidrug-resistant patients and extended beta lactamase-generating organisms were found to be susceptible to fosfomycin[13]. In a different study that examined the sensitivity of fosfomycin in MDR cases and extended-spectrum beta-lactamase-producing organisms (ESBL); a single dosage of fosfomycin (3 gm) was shown to be equally efficacious for treating uncomplicated urinary tract infections as ciprofloxacin 500 mg for five days according to a randomized controlled trial that involved 260 individuals[14]. In vitro sensitivity of common pathogens of urinary tract infections to fosfomycin was evaluated by Anand et al. in 2019 and it was discovered that the bacteria were extremely susceptible to fosfomycin[15]. The goal of the current study is to determine the local prevalence of multi-drug resistant (MDR) E. coli strains and their susceptibility to oral fosfomycin, one of the antimicrobials with the least amount of documented resistance in the literature. It will assist in establishing it as an empirical oral therapy against E. coli in urinary tract infections in both admitted and outpatient patients, as well as being safe for use in pregnant women. In contrast to earlier studies in our area that looked for E. coli sensitivity to injectable antimicrobials, this study will ascertain E. coli sensitivity to an oral antimicrobial drug like fosfomycin.

The objective of this study was to determine the frequency of multidrug-resistant E.Coli and their sensitivity to oral fosfomycin in urinary tract infections in the setting of a teaching hospital (KTH) in Peshawar, Pakistan.

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted in one of the units of the Department of Medicine, Khyber Teaching Hospital, Peshawar for a period of six months from July 18, 2020, to January 18, 2021. However, ethical approval was obtained earlier for this research work from Intitutional's ethical authority with reference number 752/ADR/KMC Dated 30-01-2020. The sample size was 179 using open epi and having 65% proportion of the population as multidrug resistance, 95% confidence level, and 5% margin of error with the help of WHO software to determine sample size[6]. A convenient consecutive sampling technique was utilized to collect the data.

The inclusion criteria for this study were: All patients with culture-proven E. Coli induced UTI (Urinary Tract Infection); patients of either gender with an age limit ranging from 18 to 60 years including pregnant women in all trimesters. To avoid confounding factors introducing bias in the study results, patients with diabetes, HIV/AIDS, a long-term steroid medication, and patients who used antibiotics within the previous 48 hours of presentation were excluded from the study.

After selection and consent, patients were asked to collect clean mid-stream urine samples. Two samples of urine were collected and then promptly transferred to the hospital laboratory for examination and inoculation on culture media for E Coli. The detected E.Coli were then checked for resistance and sensitivities against the antibiotics mentioned. The MDR strains were isolated and their sensitivity was checked against oral Fosfomycin. This whole data collection was done under the supervision of one microbiologist having at least five years of experience in the field. All information was recorded. Data obtained were entered and analyzed by the statistical package for social sciences (SPSS) version 20. Mean $\pm$ SD was calculated for numerical variables like age. Frequencies and percentages were calculated for categorical variables like gender, multidrug resistance, and oral Fosfomycin sensitivity. The sensitivity of oral Fosfomycin and multi-drug resistance was stratified among age and gender to see effect modification. The Post-modification Chi-square test was applied to keep the P-value ≤ 0.05 as significant.

RESULTS

The age range of 100 patients (56%) was from 18 to 30 years and 79 patients (44%) were from 31 to 60 years. The mean age was 37 years with SD $\pm$ 11.27. Seventy-three (41%) patients were male while 106 (59%) patients were female. Multidrug resistance among 179 patients was analyzed as 111(62%) patients documented multi-drug resistance while 68(38%) patients didn't have multidrug resistance. (Fig1) The sensitivity of oral fosfomycin with multidrug resistance of E.Coli among 111 patients was analyzed as oral fosfomycin was sensitive in 108 (97%) patients and was resistant in 3 (3%) patients. (Fig2) Stratification of the Sensitivity of oral fosfomycin and multidrug resistance concerning various variables are documented in tables 1-4.

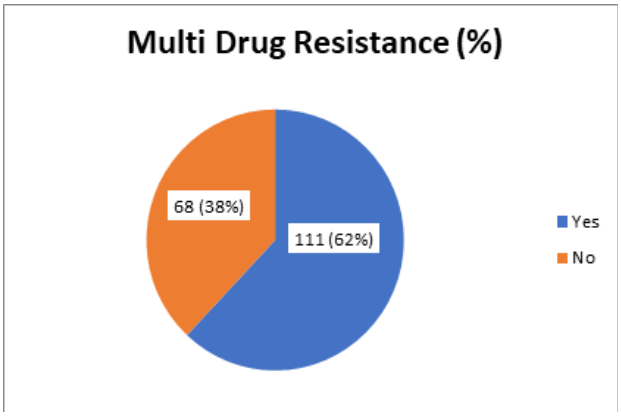

Fig 1: Multi-drug resistance of E. Coli (n= 179)

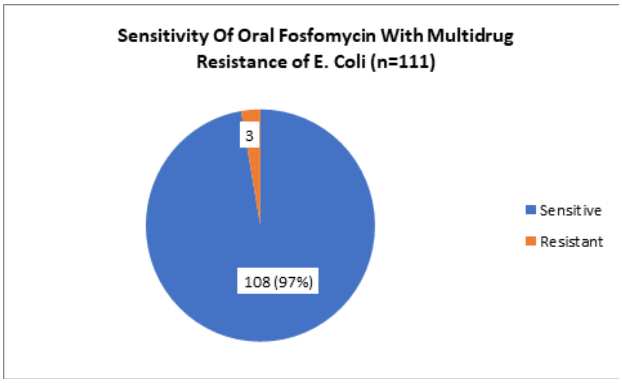

Fig 2: Sensitivity of Oral Fosfomycin against Multi-drug Resistant E. Col (n=111)

Table 1: Stratification of Multi-drug Resistance of E. Coli To Age (n=179)

Multidrug Resistance	18-30 years	31-60 years	Total	P value
Yes	62	49	111	0.9972
No	38	30	68	
Total	100	79	179	

Table 2: Stratification of Multi-drug Resistance of E. Coli To Gender (n=179)

Multidrug Resistance	18-30 years	31-60 years	Total	P value
Yes	62	49	111	0.8186
No	38	30	68	
Total	100	79	179	

Table 3: Stratification of Sensitivity of Oral Fosfomycin with Multidrug Resistance of E. Coli To Age (n=111)

Sensitivity	18-30 years	31-60 years	Total	P value
Sensitive	60	48	108	0.7022
Resistant	2	1	3	
Total	62	49	111	

Table 4: Stratification of Sensitivity of Oral Fosfomycin with Multidrug Resistance of E. Coli To Gender (n=111)

Sensitivity	Male	Female	Total	P value
Sensitive	45	63	108	0.7725
Resistant	1	2	3	
Total	46	65	111	

DISCUSSION

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide and in Pakistan as a result of the invasion and growth of microbial agents in the urinary tract. Comparatively speaking, females experience urinary tract infections at a higher rate than males. There are several UTI manifestations, ranging from mild cystitis to pyelonephritis and septicemia[16]. According to our analysis, the mean age was 37 years, with an SD of 11.27. Male patients made up 73 (41%), while female patients made up 106 (59%). Multidrug-resistant E. coli was found in 111 (62%) patients, of whom 108 (97%) were sensitive to oral fosfomycin and only 3 (3%), who had urinary tract infections, were resistant to it. According to one study by George G. et al, only 1% of E. coli has fosfomycin resistance[17].

Fosfomycin has a maximum urinary concentration of 4000 g/ml, is eliminated unchanged in the urine through glomerular filtration, and persists at quantities >100 g/ml 48 hours after a single 3-gram oral intake. Patients who are elderly, pregnant, or who have liver or renal impairment do not require dosage modifications[18]. Clinical trials have shown efficacy in AUC (Area under the curve) that is equivalent to ciprofloxacin, nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin exhibits a favorable safety profile. Guidelines and authorities from Canada, the United States, and Europe have all recom-

mended fosfomycin as a first-line treatment for AUC due to its in vitro activity against common uropathogens, including MDR isolates, as well as its favorable safety profile, which includes pregnant patients and drug interactions[19]. A study conducted by Matthews PC et al. elaborated that the MIC50 (Minimum inhibitory concentrations for 50% of the isolates) for meropenem (0.5 g/mL) and nitrofurantoin (32 g/mL) were only in the susceptible range for E. coli. The only antibiotic that completely inhibited E. coli, 70% of Klebsiella species, 50% of Pseudomonas species, 40% of Enterobacter species, and 100% of those that produced extended-spectrum beta-lactamases was fosfomycin[20]. It had a comparable impact on AmpC (Class C beta lactamases) and carbapenemase producers. The biofilms of 67% (n=141) E. coli and 74% (n=50) Klebsiella spp; were disrupted by fosfomycin. After 24 hours of incubation, fosfomycin disrupted 88% (n=27) Pseudomonas spp. and 36% (n=23) Enterobacter spp. at a concentration 2-fold dilution lower than the MIC. Fosfomycin effectively inhibited the biofilms that the MDR organisms under study here generated. The oral form of Fosfomycin was well tolerated by most patients despite the most commonly reported side effects like diarrhea, nausea, etc.[20] Unlike sulfonamide or quinolone, Fosfomycin is a safe alternative to β-lactams in the treatment of pregnant women with UTIs.

Our study is a single-centered observational research work with a limited number of patients. A large number of patients with longitudinal cohorts and multicenter randomized controlled trials across Pakistan are required for the generalization of these findings. Nonetheless, the findings are highly favorable and have a positive impact on practice-changing attitudes from the local perspective. However, prospective, longitudinal multicenter clinical trials are the need of time to generalize and validate these findings.

CONCLUSION

There is a high frequency of UTI due to multi-drug-resistant E.Coli in our setup and the majority of these MDR E. Coli infections are sensitive to oral fosfomycin.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Haider I:	Concept, Critical appraisal, and Discussion Writing
Ullah S:	Data collection, compilation of results, formatting of the article
Kalsoom B:	Data Collection, Manuscript writing
Naeem H:	Manuscript Writing, Bibliography
Ali H:	Overall compilation of the article
Khan WM:	Supervision, Critical appraisal

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.