



## SENSITIVITY OF ESCHERICHIA COLI TO FOSFOMYCIN IN PATIENTS WITH URINARY TRACT INFECTION

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### Abstract

**Objectives:** To determine the sensitivity of E. coli to fosfomycin in patients with urinary tract infection.

**Methods:** This cross-sectional study was conducted at Khyber Teaching Hospital, Peshawar, Pakistan, from 21st Oct, 2016 to 30<sup>th</sup> April, 2017 and comprised urine specimens. Biochemical techniques were used to identify Escherichia coli and antibiotic susceptibility was determined by Kirby-Bauer disk diffusion and minimum inhibitory concentration methods. SPSS 23 was used for data analysis.

**Results:** Out of 396 patients with positive urine culture for E. coli, urinary tract infection was predominant in Female population, i-e 303 (76.5%) females and 93(23.5%) males. Male to Female ratio was found to be of 1:3.2. The sensitivity of E. coli to fosfomycin was 93.9%.

**Conclusion:** Escherichia coli has a very low level of resistance against fosfomycin therefore it is suggested to be a very good choice as first line empirical treatment for urinary tract infection.

**Keywords:** Urinary tract infection, Escherichia coli, Antibiotic sensitivity, Fosfomycin.

### Introduction

Urinary tract infection (UTI) is considered as one of the most common bacterial infection worldwide<sup>1</sup> and as well as in Pakistan<sup>2</sup>. It is the second most common cause of hospital visits and have high morbidity and mortality in general population<sup>3</sup>. Urinary tract infections are far more common in women as compared to men because of their normal urogenital anatomical variation and have a 50% chance of experiencing at least one episode of UTI during their lifetime<sup>4</sup>. Presentation of UTI varies from asymptomatic pyuria to mild cystitis, pyelonephritis and septicemia<sup>5</sup>.

The microbial agents responsible for UTI have been consistent over a period of time. The most common bacterial agents causing UTI are E.coli, E.faecalis, K.pneumoniae, Pseudomonas, S.aureus and Proteus<sup>6,7</sup>. Among the uropathogens E. coli is the leading organism responsible for urinary tract infection in 85% of community acquired and 50% of hospital acquired UTIs<sup>6</sup>. Likewise, 76.6%<sup>8</sup> and 77.9%<sup>9</sup> E. coli isolates were obtained in studies conducted locally. ?

Antibiotic resistance is an emerging and serious public health problem resulting in increased morbidity and mortality. In urinary tract infections resistance rates against commonly prescribed antimicrobial agents are consistently rising<sup>10</sup>. The resistance of E. coli is increasing worldwide in community and hospital acquired infections<sup>11</sup> resulting in difficult selection of effective antibiotics<sup>12</sup>. Resistance pattern is on the rise particularly for commonly prescribed oral antibiotics in outpatient

clinics. It was 73.8% for cephadrin, 11.2% for norfloxacin, 54.2% for ciprofloxacin, 62.6% for co-amoxiclav, 66.6% for doxycycline, 69.4% for tetracycline, 50% for cefaclor and 100% for both amoxicillin and penicillin.<sup>?</sup> The development of this resistance to commonly used antibiotics has made it much difficult to treat infections and decrease the morbidity and mortality even from uncomplicated UTIs<sup>12</sup>. Among the oral antimicrobials, the susceptibility rates of E. coli are more to fosfomycin as compared to the other commonly used antibiotics <sup>?</sup>. The sensitivity of E.coli to fosfomycin was 100%, 346 E.coli isolates were all sensitive to fosfomycin<sup>Error! Reference source not found.</sup> and another study showed sensitivity of 99%<sup>13</sup>. This study aimed to find out the local prevalence of E. coli sensitivity to fosfomycin in UTI, which is an antimicrobial agent with little resistance documented so far. As fosfomycin is readily available in oral and parenteral administration in treating different bacterial infections and its relative safety in pregnancy and renal diseases might help it recommend as a first choice empirical therapy in UTI.

## Materials and Methods

This cross-sectional study was conducted at Department of General Medicine in collaboration with Microbiology Department, Khyber Teaching Hospital (KTH) Peshawar, Pakistan, from August 2019 to October 2019. Fresh midstream urine specimens were collected through aseptic measures from 396 suspected UTI cases. Patients of any age and gender who came through outpatient or inpatient departments and whose routine urine examination revealed numerous pus cells on microscopy were included. Sample selection was done through consecutive sampling technique and one urine sample was collected per patient. Specimens were cultured on MacConkey agar and blood agar media, using calibrated loop, delivering 0.01ml of the sample and incubated aerobically for 24 hours at 37°C. The plates showing significant growth as per Kass count were processed further. Identification of E. coli was done by standard method depending on observation of colony characteristics, gram-stain as well as using biochemical tests for further identification. Specimens which grew more than one type of colonies and the specimens whose age or sex record were not available were excluded. Susceptibility to antimicrobial agents was determined both by disk diffusion method of Kirby-Bauer and minimum inhibitory concentration (MIC) method on Muller-Hinton agar as described by the Clinical Laboratory Standard Institute (CLSI) 2014.12 Antibiotics used for antibiogram determination of the collected strains among FQ were: norfloxacin, ciprofloxacin, ofloxacin, enoxacin, moxifloxacin, and sparfloxacin and nalidixic acid. Other antibiotics tested were: imipenem, meropenem, tazobactam, amikacin, cefoperazone, sulbactam, gentamicin, cefepime, ceftazidime, coamoxiclav, ticarcillin, aztreonam, cefoperazone, cotrimoxazole, cefotaxime, cefixime, ceftriaxone, piperimic acid and ampicillin.

SPSS Version 23 was used for data analysis. The subjects were divided into four age groups and comparison among the groups was made using chi-square test with significant P-value of < 0.05 and 95% Confidence Interval.

## Results

In this study 396 patients were included who suffered from culture proven E. coli induced UTI. Out of 396 patients 303 (76.5%) were females while 93(23.5%) were male with a male to female ratio of 1:3.2.

Patients age ranged from 18 to 60 years were included in the study with an average age 45.31 years  $\pm$  12.70 SD.

Patients age was divided into two categories; i-e; 18 to 40 years representing young sexually active group, while the second category included patients from 41 to 60 years of age; representing older subjects. The first category had 138 (34.48%) patients while the second category had 258 (65.15%). Out of 396 E. coli isolates 372 (93.9%) were sensitive to fosfomycin while 24 (6.1%) were found resistant to it. Gender wise distribution of E. coli sensitivity to fosfomycin showed that out of 303 females 287 (94.7%) were sensitive and 16 (5.28%) were resistant.

In male population, out of 93, 85 (91.3%) were sensitive and 8 (8.6%) were resistant but the difference was statistically not significant among genders (p value 0.240).

Results of *E. coli* sensitivity in different age groups was; from 18 to 40 years, out of 138, 130 (94.2%) were sensitive and 8 (5.8%) were resistant. In age group 41 to 60 years, out of 258, 242 (93.8%) were sensitive and 16 (6.2%) were resistant but with no statistically significant difference (p value 0.872).

## Discussion

UTI is one of the most common health issues both in the community and hospital settings [98], responsible for significant high mortality and morbidity worldwide. [99] Its Prevalence varies among different age groups, gender, patients having co-morbidities like diabetes mellitus, structural abnormalities, indwelling catheters, pregnancy, renal failure, urolithiasis, male sex, voiding dysfunction, polycystic kidneys, childhood, immunosuppression, diagnostic history of urinary tract surgery [38], and interventions like cystoscopy and urethral catheterization.

Did our study support the findings of previous studies or not?

An increasing number of urinary tract infections (UTIs) are due to drug-resistant pathogens for which there are limited treatment options available especially for outpatient. Fosfomycin is a phosphonic acid derivative which is available in the United States as a powdered sachet approved by the Food and Drug Administration and other countries as well, for the treatment of uncomplicated UTIs in both women and men. Fosfomycin is a broad-spectrum antimicrobial and having activity against Gram-positive and Gram-negative bacteria. Recent studies show in vitro activity against MDR pathogens, including carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp), *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase (ESBL)-producing bacteria, and vancomycin-resistant enterococci (VRE) [100]. However, clinical data for the use of fosfomycin for the treatment of UTIs due to drug resistance pathogens are limited especially MDR. Fosfomycin available both for inpatient and outpatient basis has somehow retained sensitivity against *E. coli* in UTI. Due to limited side effects, easy availability and cost effectiveness it is now used worldwide as empirical therapy.

The study was aimed to have knowledge about the sensitivity of *E. coli* the most common bacteria responsible for causing urinary tract infection to fosfomycin, which is one of the first line therapy for uncomplicated UTI, easily available and cheap as well. It is important to determine the sensitivity pattern in order to have an insight of the local disease and drug resistance burden which varies according to the population being studied, from time to time and also according to geographical location [101].

In this study it was reported that UTI was more common in females compared to males with male to female ratio of 1:3.2 in both age groups. Shabbir *et al* (2017) reported that UTI to be more common in females than males [102] and in another study by Betsy Foxman [49]. Though it is reported that UTI is more common in men at extreme of ages due to hypertrophy of the prostate in old age [103], while congenital abnormalities in young children but no comparison was done in these age groups because they were excluded from the study.

Sensitivity of *E. coli* to fosfomycin determined in our study was 93.9%. In a study conducted in Korea the sensitivity of *E. coli* to fosfomycin was 100%, 346 *E. coli* isolates were all sensitive to fosfomycin [26] and other studies showed sensitivity of 99% [104] and 95.5% respectively [105]. As compared to fosfomycin the resistance to other oral antibiotics is very high. It was 73.8% for cephadrin, 11.2% for norfloxacin, 54.2% for ciprofloxacin, 62.6% for co-amoxiclav, 66.6% for doxycycline, 69.4% for tetracycline, 50% for cefaclor and 100% for both amoxicillin and penicillin [17].

Patients were divided in two age groups, sexually active group and sexually non-active group. *E. coli* sensitivity to fosfomycin was 94.2% in sexually active group and it was 93.8% in sexually non-active group. There was statistically no significant difference in the sensitivities of *E. coli* to fosfomycin between the two groups.

In our study the *E. coli* growth was more common in females than in males but in the sensitivity pattern of *E. coli* to fosfomycin there was no significant difference between the genders. It is concluded that activity of fosfomycin against *E. coli* is the same in all age groups and among genders. The growth of Extended Spectrum Beta-lactamase-producing (ESBL) *E. coli* was 16.91% in our study with sensitivity to fosfomycin was 94.02%. Beta-lactamases ( $\beta$ -lactamases, also known as penicillinase) are enzymes produced by different type bacteria that result in multi-resistance to  $\beta$ -

lactam antibiotics such as penicillins, cephalosporins, cephamycins, and carbapenems (ertapenem), although carbapenems are relatively resistant to beta-lactamase. Beta-lactamase causes antibiotic resistance by breaking the antimicrobial structure. These antimicrobials all have a common element in their molecular structure: a four-atom ring known as a  $\beta$ -lactam. It is through hydrolysis that the lactamase enzyme breaks the  $\beta$ -lactam ring open, making them ineffective. Beta-lactam antimicrobials are typically used to treat a broad spectrum of Gram-positive and Gram-negative bacteria. Beta-lactamases produced by Gram-negative organisms are usually secreted, especially when antibiotics are present in the environment [106]. Arslan *et al* reported an ESBL growth rate of 7.9% in *E. coli* strains recovered from community-acquired UTI in 514 patients [107]. As evident from our study fosfomycin resistance is very rare in ESBL-producing *E. coli* strains. A resistance rate of 3.5% to fosfomycin has been reported by Pullukcu *et al* in ESBL-producing *E. coli* strains [108]. But the fosfomycin sensitivity of ESBL-producing *E. coli* was not having any statistically significant difference to non-ESBL producing *E. coli*.

Our study shows that fosfomycin is a good choice as an empirical therapy for uncomplicated urinary tract infections and can be used in both inpatients and outpatients.

Study limitations?

### Conclusion

Urinary tract infection is a common health problem and with high levels of antibiotics resistance, it is likely that disease can become more prevalent. Therefore, it calls for continuous monitoring of antibiotic resistance for selection of appropriate antibiotics therapy. Strict knowledge about the sensitivity patterns of bacteria and appropriate use of antibiotics is highly warranted. Resistance to antimicrobials is on rise and only limited option of oral antibiotics are available particularly to treat urinary tract infection on outpatient basis. This study concluded that *E. coli* is highly sensitive to fosfomycin in both in and outpatients with UTI. Due to its limited side effects, easy availability and cost effectiveness, fosfomycin is a very good choice as first line empirical treatment for urinary tract infection.

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