

# Fosfomycin an Old Drug with A New Role in E.Coli Associated Urinary Tract Infections

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## ABSTRACT

**Objective:** To know the impact of Fosfomycin an Old Drug with A New Role in E.Coli Associated Urinary Tract Infections.

**Study Design:** Descriptive Study

**Place and Duration of Study:** This study was conducted at the department of Nephrology Khyber Teaching Hospital, Peshawar from July 2020 to June 2021 for a period of one year.

**Materials and Methods:** Urine Culture Sensitivity of patients with UTI was assessed and E. Coli sensitivity pattern was studied.

**Results:** Over all sensitivity of E. coli to Fosfomycin was 84.31% in the studied population. According to gender distribution of the cohort the sensitivity to Fosfomycin was 83.33% in male patients and 84.84% in the female patients. To compare the sensitivity of Fosfomycin versus other antibiotics in UTI, we found that Fosfomycin was showing sensitivity against E. coli related UTI of 84.31% compared to that Ciprofloxacin 20.58%, Trimethoprim sulphamethoxazole 17.64% and Amoxicillin-clavulanic acid 13.72%.

**Conclusion:** This study shows that in the presence of mounting antibiotics resistance, Fosfomycin is a safe and suitable alternative in the treatment of UTI caused by MDR pathogens like E. Coli which otherwise do not respond to other antibiotics.

**Key Words:** UTI, E. Coli, Fosfomycin

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## INTRODUCTION

Urinary tract infections (UTI) are among the commonest types of bacterial infections worldwide. More than 10 million out patients visit and 2 million emergency room visit occurs annually in USA due to UTIs<sup>1,2</sup>

Antimicrobial resistance is increasing worldwide, leading to infections that are difficult to treat and are associated with higher morbidity and mortality. The treatment of UTI with these resistant organisms is a challenge for the practicing Physicians and Nephrologists.

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The misuse and over use of these antibiotics have led to the emergence of resistant strains of bacteria specially the Escherichia Coli (E, Coli) which is the most common pathogen isolated from urine cultures world over. There are few new antibiotics on the horizon and those that have been approved recently are mostly for intravenous use, therefore older 'forgotten' drugs are being re-explored for the treatment of UTI and cystitis<sup>3,4,5,6</sup>

Fosfomycin is a broad spectrum bactericidal antibiotic and an acceptable alternative drug in such cases is available in oral form, is well tolerated and has low resistance rates in E. Coli based UTI, having little interaction with other drugs.<sup>7</sup> Based on the efficacy, safety and well tolerability, the 2011 Infections Disease Society of America (IDSA) and FDA clinical practice guidelines endorsed Fosfomycin as a first line treatment for uncomplicated UTI and cystitis.<sup>8,9,10,11</sup>

This drug was used for a long time in the past for treatment of UTI, but gradually lost its favor due to emergence of newer antibiotics in the market. However, with the emergence of resistance to different antibiotics such as B Lactam antibiotics, quinolones and aminoglycosides worldwide, Fosfomycin is again emerging as a viable alternative option.<sup>12,13</sup> Data from Spain showed the overall resistance level to all types of Escherichia Coli (E, Coli) isolated (ESBL producing and ESBL non-producing) to Fosfomycin remained

significantly low at 2.9% in 2019. Similarly, data from Poland showed the overall susceptibility of *E. Coli* isolates to Fosfomycin were 62.2% in complicated UTIs and 77.6% in uncomplicated UTIs.<sup>14,15,16</sup>

Similarly another study at Dutch hospitals showed resistance rates of 14% for ciprofloxacin, 23% for trimethoprim-sulphamethoxazole and 36% for amoxicillin-clavulanic acid with higher resistance rates in patients having UTI due to *E. Coli* uropathogens.<sup>17</sup>

Fosfomycin disodium is very hydrophilic agent therefore only 3% of drug is bound to protein in serum and this permits favorable tissue availability. Also, the low molecular weight favors higher diffusibility as well.<sup>18,19</sup> Approximately 93% of administered dose undergoes the glomerular filtration in the kidney and is excreted unchanged in urine.<sup>20</sup> A small number of adverse effects, like nausea, vomiting abdominal colic, diarrhea and dyspepsia have been reported following oral usage.<sup>21</sup> In preventing different stages of cell wall synthesis Fosfomycin may have synergistic effect with B Lactam antibiotics because Fosfomycin prevents the first stage of cell wall synthesis, while B-Lactam antibiotics inhibits the final phase of it.<sup>22</sup>

Therefore, this old forgotten drug is now emerging again for the treatment of *E. coli* associated UTIs and cystitis. It also has a unique property of not sharing any structural similarity and lack of cross-resistance with other antibiotics.<sup>23</sup>

## MATERIALS AND METHODS

This is a descriptive study conducted over a period of one year from July 2020 to June 2021 in the department of Nephrology Khyber Teaching Hospital, Peshawar. The study was approved by the institutional ethical committee.

Urine sample of patients received in Out Patient Department of Nephrology, with signs and symptoms of UTI, were sent for culture & sensitivity in the above-mentioned period. Urine sample received in the Microbiology Laboratory from these patients were plated by semi-quantitative culture method on blood agar and MacConkey's agar and incubated at 37°C overnight. The isolates obtained from the samples with significant bacteremia with the background of relevant supportive clinical features of UTI were processed further. The bacterial species identification was performed by standard biochemical methods.<sup>24</sup>

Inclusion criteria used to define patients with UTI caused by *E. Coli* were:

1. Signs and symptoms of UTI (for example dysuria, urgency, suprapubic tenderness, fever and hematuria or pyuria.)
2. Urine culture positive for *E. Coli* >10<sup>5</sup> colony forming units/ml in a clean-catch, midstream urine sample.
3. In vitro susceptibility of *E. Coli* to Fosfomycin as determined by the agar-dilution method and

according to European committee on antimicrobial susceptibility testing (EUCAST) criteria.

## RESULTS

Out of 102 patients studied during this period 36 (35.29%) were male and 66 (64.70%) were female patients, with male to female ratio of 1:1.8 (Table 1). Patient age was in the range of 12 years to 80 years with mean of 54 years.

Over all sensitivity of *E. Coli* to Fosfomycin was 86 out of 102 (84.31%) in the studied population. (Table 2).

According to gender distribution of the cohort the sensitivity to Fosfomycin was 30/36 (83.33%) in male patients and 56/66 (84.84%) in the female patients (Table 3).

Regarding age wise distribution of culture positive UTI 9/102 (8.82%) were less than 25 years of age, 52/102 (50.90%) were in the age range of 25-50 years and 56/102 (54.90%) were above 50 years of age (Table 4).

In the Fosfomycin sensitivity spectrum we found that 9/9 (100%) patients were sensitive in the age group of less than 25 years, while 33/52 (63.46%) were in the age group of 25-50 years and remaining 44/56 (78.57%) were patients above 50 years of age (Table 5). To compare the sensitivity of *E. Coli* to Fosfomycin versus other antibiotics commonly used in the community, we found that Fosfomycin was showing sensitivity in 86/102 (84.31%) as mentioned earlier and compared to that Ciprofloxacin 21/102 (20.58%), Trimethoprim-sulphamethoxazole 18/102 (17.64%) and Amoxicillin-clavulanic acid 14/102 (13.72%) showed low level of sensitivity against the *E. Coli* in urine culture (Table 6).

**Table No.1: UTI Occurance in Different Gender**

Characteristic	No	Percentage
All patients	102	100%
Male	36	35.29%
Female	66	64.70%

**Table No.2: Total Positivity Ratio**

Positive cultures	Negative cultures
86 (84.31%)	16 (15.68%)

**Table No.3: Gender Distribution among Positive Cases**

Characteristics	Positive cultures	Negative cultures	Total
Male	30	6	36 (83.33%)
Female	56	10	66 (84.84%)

**Table No.4: Age Wise Distribution of Culture Positive UTI**

Age range	No	Percentage
Less than 25 years	9/102	8.82%
25-50 years	38/102	37.25%
More than 50 years	56/102	54.90%

**Table No.5: Sensitivity in Different Age Groups**

Age range	Total patients	Positive cultures	Percentage
Less than 25 years	9	9	100%
25-50 years	52	33	63.46%
More than 50 years	56	44	78.57%

**Table No.6: Sensitivity Pattern Against E. Coli in Different Antibiotics**

Drugs	Positivity against E. Coli	Percentage
Fofomycin	86/102	84.31%
Ciprofoxacin	21/102	20.58%
Trimethoprim sulphamethoxazole	18/102	17.64%
Amoxicillin clvulanic acid	14/102	13.72%

## DISCUSSION

Our study showed that urinary tract infections (UTI) in females were 64.70% as compared to males 35.29%. Usually, 60% of all females will develop UTI in their life time. In our study it was shown that 54% of patients with UTI were above 50 years of age compared to 37% patients having UTI in the age group of 25-50 years. The Fosfomycin sensitivity ratio in E. Coli related UTI was found to be more than 84% which was significantly better than most of the commonly used drugs. In the positive cohort of almost 100% cases in younger age group of less than 25 years showed sensitivity to Fosfomycin, while 78% of patients above 50 years of age were sensitive to Fosfomycin against E. Coli related UTI.

The overall sensitivity of Fosfomycin against E. Coli was 84% in our study and it was also compared to the other commonly prescribed antibiotics. The sensitivity of ciprofloxacin against E. Coli was only 20%, trimethoprim-sulphamethoxazole was 17% and amoxicillin-clavulanic acid was only 13% which showed significant resistance against this commonly found uropathogen. Ciprofloxacin is still mostly prescribed in OPDs for the treatment of UTIs, along with significant number patients getting the other two antibiotics as mentioned above. This overuse has led to the emergence of significant resistance to these commonly prescribed drugs.

Fosfomycin demonstrated potent in-vitro activity against E. Coli along with other common uropathogens.<sup>24</sup> Antimicrobial resistances to Fosfomycin is rare in E. Coli (1-3%) as compared to fluoroquinolones and trimethoprim-sulphamethoxazole (>20%)<sup>25</sup>. This finding is in keeping with our study pattern of sensitivity against this old but re-emerging drug.

In our study we have shown high amount of resistance to the other commonly prescribed antibiotics against frequently occurring uropathogen like E. Coli. This is similar to what has been described by different researchers in various studies<sup>17,26-28</sup>. Various studies from our neighboring country India has also revealed similar pattern of resistance<sup>29,30</sup>. The data from our study regarding high Fosfomycin sensitivity against E. Coli has also been demonstrated in different studies worldwide<sup>28-30</sup>. For example, Gupta et al showed 52.6% of isolates from UTI were ESBL producer and all of these strains were susceptible to Fosfomycin<sup>31</sup>. Similarly, according to Rejendran et al, Fosfomycin was the only antibiotic that effectively inhibited most strains of E. Coli including MDR strains<sup>32</sup>. In another study by Karlowsky et al, they have reported significant susceptibility against E. Coli collected from 2010 to 2013 as part of Canadian National Surveillance Study CANWARD<sup>33</sup>.

Due to its good renal excretion, Fosfomycin concentration in urine is very high which enhances its ability to break up the biofilms due to catheters. This was determined by Gopichand et al in their study and they have concluded that Fosfomycin could inhibit biofilm formation<sup>34</sup>. Regarding tolerability, different clinical trial has shown well tolerability and good compliance of this orally effective drug<sup>35-37</sup>.

As an oral antibiotic with fewer side effects, and a broader spectrum of antibacterial activity that includes different strains of E. Coli, Fosfomycin has the potential to improve patients' quality of life while minimizing health care cost and easily availability.

## CONCLUSION

This study shows that in the presence of mounting antibiotics resistance, Fosfomycin is a safe and suitable alternative in the treatment of UTI caused by MDR pathogens like E. Coli which otherwise do not respond to most of the available antibiotics.

### Author's Contribution:

Concept & Design of Study:	Shandana Altaf
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**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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