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Fosfomycin—A Promising Oral Antibiotic for the Treatment of Urinary Tract Infection (UTI)

Sadia Sharmin[1], Sheikh Mohammed Mostofa Kamal[1], Md. Alimur Reza[2], Khandokar Mohammad Ashik Elahi[2], Sheikh Mohammed Mostofa Elma[3], Bushra Habib[2]

[1]Department of Microbiology, Anwer Khan Modern Medical College Hospital, Dhaka, Bangladesh
[2]Department of Medical Affairs, Beximco Pharmaceuticals Limited, Dhaka, Bangladesh
[3]Department of Pharmacology, Anwer Khan Modern Medical College Hospital, Dhaka, Bangladesh
Email: ake@bpl.net

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Abstract

Background: Among the common morbid causes that are prevalent among all age groups, urinary tract infections top the list. In our country, most of the UTI patients visiting hospitals (OPD or IPD) are already on empirical antibiotics even before getting the sensitivity report in their hand. The purpose of this research was to examine the susceptibility patterns of commonly used antibiotics, particularly fosfomycin, against common uropathogens. **Methodology:** This was a prospective observational study conducted between January and March 2021 in four private tertiary hospitals in Dhaka, Bangladesh. All the urine samples referred to these four laboratories, obtained from patients of all ages and both genders, clinically diagnosed to have UTI, were included. Urine culture was performed by a semiquantitative method on blood agar media and MacConkey agar media. Following identification, antimicrobial sensitivity testing was performed using the modified Kirby Bauer disk diffusion method in accordance with CLSI standards. The data was put into Statistical Package for Social Sciences (SPSS) statistical software version 25 for the analysis. **Results:** A total of 5389 urine samples were received from four private hospitals in Dhaka over three months, and of these, 934 (17.33%) isolates were obtained from culture. About 95% of the isolates were gram-negative bacilli (GNBs). The most common isolate was *Escherichia coli* 615 (65.85%), followed by *Klebsiella* spp. 154 (16.49%), *Pseudomonas* spp. 64 (6.85%) and 51 (5.46%) isolates of Enterobacter. Among the gram-positive cocci, the most common were *Enterococci fecalis* 18 (1.93%) and *Staphylococcus aureus* 17 (1.82%). Of all the antibiotics tested, fosfomycin sensitivity was 98.4%, 88.88%, and 100% for *Escherichia coli*, *Enterococci fecalis*, and *Staphylococcus aureus*, respectively. All the isolates tested were susceptible to Meropenem (77% - 100%), Amoxiclav (78% - 100%) and Nitrofurantoin (45% - 94%). Sensitivity amongst all the uropathogens for ceftriaxone, ciprofloxacin, and co-trimoxazole was nearly 50% - 77%. **Conclusion:** The positivity of urinary isolates is 17.33%, with the most common pathogen being *Escherichia coli*. Common uropathogens show the highest *in vitro* susceptibility to fosfomycin. So, fosfomycin should be considered as a highly potent and promising alternative oral antibiotic treatment for UTI.

Keywords

Antibiotic Susceptibility, Fosfomycin, Urinary Tract Infections

1. Introduction

Urinary tract infection (UTI) is one of the most prevalent infections diagnosed among all ages. Globally, about 150 million patients are infected with UTI every year, which may rise to 75% among females by the age of 24, and 15% - 25% of this group may suffer from recurrent UTI [1] [2] [3]. A urinary tract infection (UTI) is an infection of the bladder (cystitis) or the kidneys (pyelonephritis), and it could be either hospital-acquired or community-acquired. UTI is a morbid disease, causing loss of working days and treatment cost burden [4]. They are also an important source of sepsis, resulting in high mortality rates. Pregnancy, extreme age, spinal cord injuries, diabetes, multiple sclerosis, acquired immunodeficiency disease syndrome, or underlying urologic abnormalities increase the risk of UTI. In addition, catheter-associated UTI is the most common health care associated infection [2].

Escherichia coli is the most common causative agent of UTI in both hospital and community acquired infections showed by many previous studies. Hospital acquired UTI is associated with a higher prevalence of Enterococci and Coagulase-Negative Staphylococci [5] [6] [7]. Besides, *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *Staphylococcus aureus*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Enterobacter cloacae* and *Proteus mirabilis* have also been identified as etiologic agents of UTI [2]. In terms of reduction in complication, mortality rates and overall treatment costs, it is crucial to accurately identify and isolate bacterial uropathogens and also ascertain their antibiotic drug susceptibility.

However, the increasing emergence of bacterial resistance to a large number of antibiotics and lack of development of new antibiotic is causing major health concerns worldwide. Antibiotic use is the single most important modifiable risk factor for antibiotic resistance [8]. Several antibiotics are used for the treatment of UTIs, of which co-trimoxazole, fluoroquinolones, β-lactam antibiotics and nitrofurantoin are most commonly used [9] [10]. The 2010 IDSA guidelines recommend using nitrofurantoin and cotrimoxazole as first-line agents, followed by fosfomycin, fluoroquinolones, and β-lactam agents as second-line agents for uncomplicated UTI [11]. Fosfomycin trometamol is recommended as a single

3-g dose as a first-line treatment in some other international guidelines for the treatment of uncomplicated urinary tract infections [12] [13]. Surveillance reports demonstrate high rates of fosfomycin susceptibility, even among emergent multidrug-resistant (MDR) uropathogens [14] [15] [16] [17] [18]. As bacterial resistance to frequently used antibiotics (especially TMP/SMX, fluoroquinolones and β-lactam antibiotics) is rising, there is an increasing need for evidence-based prescribing. In the era of rising antimicrobial resistance seen globally, there is renewed interest in fosfomycin as an attractive therapeutic option [19]-[24].

Fosfomycin trometamol is an old, off-patent oral antibiotic, recommended as a single dose and well excreted in the urine [25] [26]. Most of the available literatures on fosfomycin resistance on *E. coli* according to CLSI guidelines [27] have fosfomycin zone diameter for Enterobacteriaceae and *Enterococcus* spp. only. There are a few studies [28] that have studied fosfomycin resistance in all gram-positive and gram-negative isolates. In the context of Bangladesh, fosfomycin for the treatment of UTI is not used very randomly, its potential has not been explored fully, and there is a lack of scarcity of data about this drug here. So, in view of the limited availability of novel antimicrobial agents, the reevaluation of older antibiotic agents seems to be an appealing option.

In this study we identify the common bacterial pathogens of Urinary Tract Infection (UTI) in four private hospitals of Dhaka, Bangladesh and determine the susceptibility of commonly used antibiotics for the treatment of UTI including fosfomycin as a new option because of uncontrolled and widespread use of antibiotics, the resistance pattern of uropathogens is changing drastically, specifically in developing countries like Bangladesh which is causing treatment failure.

2. Material and Methods

Study Area and Population—From January to March of 2021, urine samples were referred from both OPD (outpatients departments) and IPD (inpatients departments) at four private hospitals in Dhaka, Bangladesh (two from the south city corporation and two from the north city corporation). A total of 5389 urine samples were referred for culture during the study period. We included all with their consent, who were referred by a physician with the suspicion of UTI irrespective of their age, sex or physical condition. All the patients were tested between January and March 2021 in four private tertiary hospitals selected as study center in Dhaka, Bangladesh.

Sample Collection—All the patients were instructed very clearly to collect the urine sample aseptically to prevent contaminations from the urethra. So, clean-catch midstream urine and catheter urine was collected aseptically into a 10 ml sterile screw-capped container with proper labeling and transported to the laboratory for analysis.

Sample Processing—A calibrated loop technique was used to isolate bacterial pathogens from urine samples. A sterile loopful urine sample was inoculated into blood agar media and MacConkey agar media (Oxoid, UK). The injected culture plates were incubated for 24 hours at 370 degrees Celsius. If the colony count was 105 CFU/mL or 104 CFU/mL and >5 pus cells per high-power field, the sample was ruled positive for UTI. Then the isolated bacteria were identified using standard microbiological methods up to genus and species level wherever applicable [29]. Urine samples that yielded multiple bacterial pathogens were subject to repeated culture to get pure culture.

Antibiotic Susceptibility Testing—Bacterial isolates were tested for antibiotic susceptibility testing by the standard Modified Kirby Bauer's disc diffusion method [30]. The zone of inhibition was measured and evaluated according to clinical and laboratory standards after 24 hours of incubation of Mueller Hinton agar plates at 300C with the antibiotic disc [27]. Fosfomycin (Fo), Amoxicillin/Clavulanate (AMC), Ciprofloxacin (CIP), Ceftriaxone (CRO), Meropenem (MEM), Nitrofurantoin (F), and Co-trimoxazole were used as standard antibiotic discs for the isolates in this study (CTX). In this investigation, standard strains of *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), and *P. aeruginosa* (ATCC 27853) were employed as a reference.

Method of data quality assurance and data analysis—After the collection of data, all questionnaires were checked for completeness, correctness and internal consistency to exclude missing or inconsistent data and those were discarded. Corrected data were entered into the Statistical Package for Social Sciences (SPSS) statistical software version 25 for the analysis. Quantitative variables were summarized by mean and standard deviation. On the other hand, qualitative variables were summarized by percentage. Necessary bivariate analysis and statistical tests were done.

3. Result

A total of 5389 urine samples were received from OPD and IPD patients of four hospitals, who were referred by their concern physicians with suspected UTI, over 3 months and of these, 934 (17.33%) isolates were obtained from the samples (**Figure 1**). Among these 934 isolates, 687 (73.56%) were female and 247 (26.44%) were male. Among female participants 18% had culture growths, whereas among male participants 10% had positive culture growths (**Figure 2**). The highly affected age groups were less than 15 years and more than 64 years (**Table 1**). In (0 - 14) age group 15.52% participants and in (>64) age group 24.19% had positive culture growth, whereas (15 - 24) age group had the lowest percentage of culture growth (8.45%) (**Table 1**). Around 95% of the isolate were gram-negative bacilli (GNBs). The most common isolate was *E. coli* 615 (65.84%), followed by *Klebsiella* spp. 154 (16.49%), *Pseudomonas* spp. 64 (6.8%) and 51 (5.46%) isolates of Enterobacter. Among the Gram-positive cocci, the most common were *Enterococcus fecalis* 18 (1.9%) and *Staphylococcus aureus* 17 (1.82%). There were also few isolates of Proteus, Acinatobacter, *S.saprophyticus* and *S.agalaticae.* The profile of the pathogens causing UTI is shown in (**Figure 3**). The susceptibility of the

GNBs and GPCs (*Staphylococcus* spp. and *Enterococcus* spp.) to the various antibiotics tested is shown in (Table 2).

Table 1. Distribution of cases of UTI in different age groups (n = 934).

Age	*E. coli* n (%)	Klebsiella n (%)	Pseudomonas n (%)	Enterobacter n (%)	Enterococci n (%)	Proteus n (%)	*S Saprophyticus* n (%)	*S. aureus* n (%)	Acinatobacter n (%)	*S. agalactiae* n (%)	Total n (%)
0 - 14	102 (70.3%)	22 (15.2%)	5 (3.5%)	15 (10.3%)	1 (0.7%)	0 0	0 0	0 0	0 0	0 0	145 (15.52%)
15 - 24	57 (72.2%)	15 (19%)	1 (1.3%)	2 (2.5%)	0 0	0 0	0 0	3 (3.8%)	1 (1.2%)	0 0	79 (8.45%)
25 - 34	83 (70.3%)	17 (14.4%)	6 (5.1%)	5 (4.2%)	2 (1.7%)	0 0	0 0	4 (3.4%)	0 0	1 (0.8%)	118 (12.63%)
35 - 44	79 (69.9%)	16 (14.2%)	4 (3.5%)	5 (4.4%)	4 (3.5%)	2 (1.8%)	1 (0.9%)	2 (1.8%)	0 0	0 0	113 (12.09%)
45 - 54	75 (65.8%)	20 (17.5%)	7 (6.1%)	6 (5.3%)	1 (0.9%)	2 (1.7%)	1 (0.9%)	2 (1.7%)	0 0	0 0	114 (12.20%)
55 - 64	83 (59.7%)	30 (21.6%)	12 (8.6%)	10 (7.2%)	1 (0.7%)	1 (0.7%)	0 0	1 (0.7%)	1 (0.7%)	0 0	139 (14.88%)
>64	136 (60.2%)	34 (15%)	29 (12.8%)	8 (3.5%)	9 (4%)	5 (2.2%)	0 0	5 (2.2%)	0 0	0 0	226 (24.19%)
Total	615 (65.84%)	154 (16.5%)	64 (6.8%)	51 (5.46%)	18 (1.9%)	10 (1.1%)	2 (0.21%)	17 (1.8%)	2 (0.21%)	1 (0.1%)	934 (100%)

Table 2. Antimicrobial susceptibility (% sensitivity) of isolated uropathogen.

Isolates	Fosfomycin N (%)	Meropenam N (%)	Amoxiclav N (%)	Nitrofurantoin N (%)	Ceftriaxone N (%)	Ciprofloxacin N (%)	Co-trimoxazole N (%)
Escherichia coli (N = 615)	605 (98.4%)	567 (92.2%)	517 (84.1%)	524 (85.2%)	332 (53.9%)	327 (53.2%)	325 (52.8%)
Klebsiella (N = 154)	85 (55.2%)	145 (94.1%)	121 (78.6%)	81 (52.6%)	99 (64.3%)	113 (73.4%)	104 (67.5%)
Enterobacter (N = 51)	36 (78.6%)	49 (96.1%)	44 (86.3%)	31 (60.8%)	23 (45.1%)	31 (60.8%)	29 (56.8%)
Pseudomonas (N = 64)	47 (73.6%)	50 (78.1%)	40 (62.5%)	29 (45.3%)	22 (34.3%)	41 (64.1%)	25 (39.1%)
Proteus (N = 10)	10 (100%)	10 (100%)	9 (90%)	4 (40%)	9 (90%)	5 (50%)	3 (30%)
Acinatobacter (N = 2)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50)	2 (100%)
Enterococcus fecalis (N = 18)	16 (88.88%)	14 (77.8%)	16 (88.9%)	11 (61.1%)	10 (55.6%)	9 (50%)	14 (77.8%)
S. aureus (N = 17)	17 (100%)	17 (100%)	17 (100%)	16 (94.11%)	13 (76.47%)	6 (35.3%)	9 (52.9%)
S. saprophyticus (N = 2)	1 (50%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)
S. agalactiae (N = 1)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	0	1 (100%)

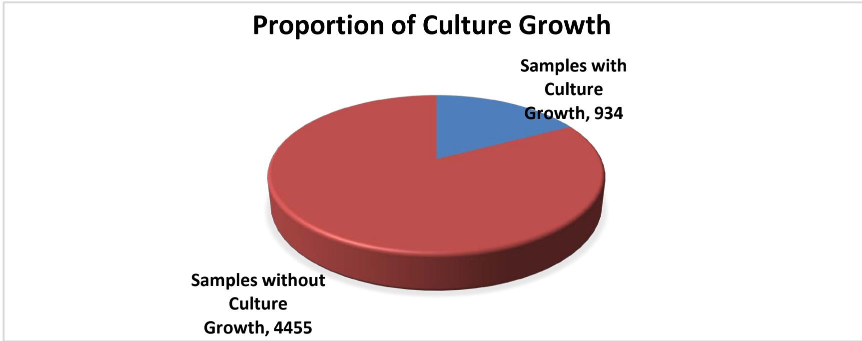

Figure 1. Proportion of culture growth found in total sample (n = 5389).

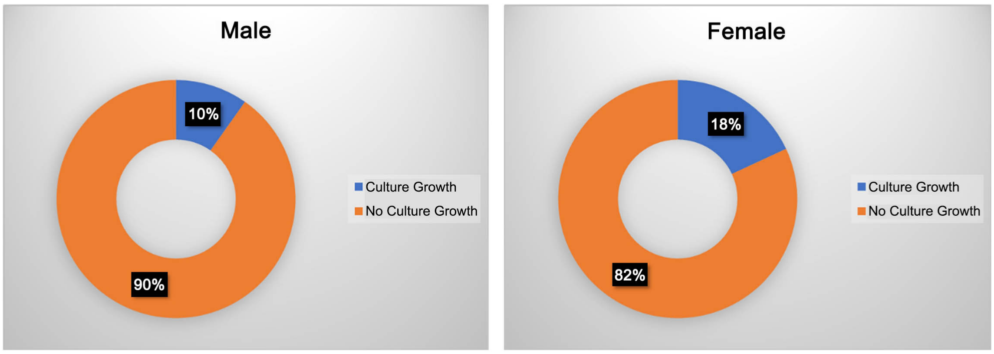

Figure 2. Proportion of culture growth according to gender.

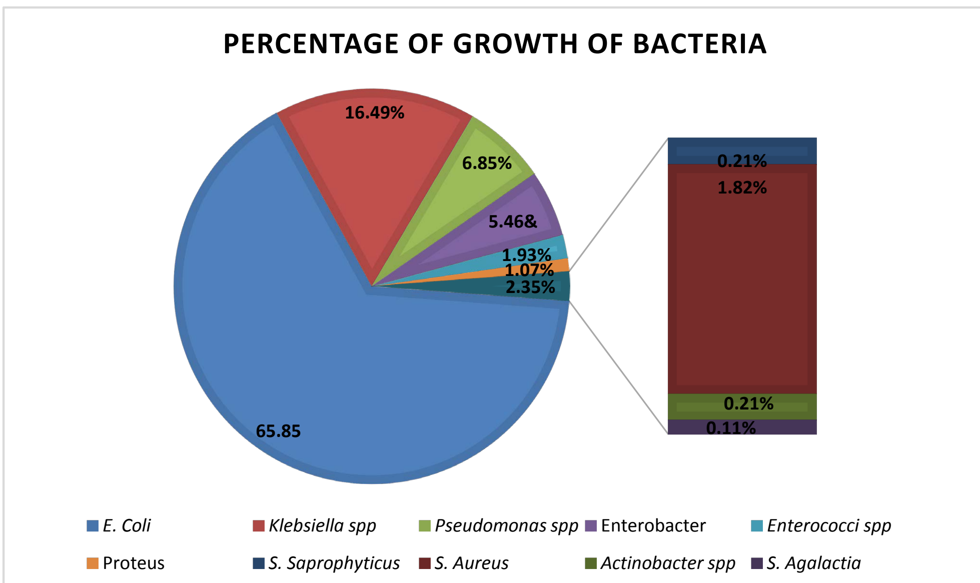

Figure 3. Distribution frequency of isolated bacterial uropathogen (n = 5389).

The most common *Escherichia coli* was predominantly sensitive to fosfomycin 605 (98.4%), meropenam 567 (92.2%), nitrofurantoin 524 (85.2%), amoxicillin/clavulanate 517 (84.1%), to a lesser extent to ceftriaxone (53%), ciprofloxacin (53.2%) and cotrimoxazole (52.8%). Among the 154 isolates of *Klebsiella* spp., the majority were susceptible to meropenam 145 (94.15%) and 85 (55.2%) isolates were susceptible to fosfomycin. Among the 64 isolates of *Pseudomonas* spp. 50 (78.1%) isolates were susceptible to meropenem and 47 (73.6%) isolates were susceptible to fosfomycin. Comparatively lower susceptibility rates were seen against nitrofurantoin (45.3%), ceftriaxone (34.3%) and cotrimoxazole (39.1%). Among 51 isolates of Enterobacter, meropenem showed the highest susceptibility 49 (96.1%) followed by amoxiclav 44 (86.34%) and Fosfomycin 36 (78.6%). Ceftriaxone and co-trimoxazol showed the lowest sensitivity of 23 (45.1%) and 29 (56.8%) respectively. Among the 18 *Enterococcus* spp.., high susceptibility was seen against fosfomycin (88.88%), meropenem (77.78%), amoxicillin/clavulanate (88.88%) and cotrimoxazole (77.78%). All *Staphylococcus aureus* isolates (100%) were susceptible to fosfomycin, meropenem and amoxicillin/clavulanate and to a lesser extent to nitrofurantoin (94.11%). After testing all the antibiotics in all the isolates, fosfomycin was found to be most sensitive followed by meropenem, amoxicillin/clavulanate and nitrofurantoin for all the isolates tested. Besides, ceftriaxone, ciprofloxacin and co-trimoxazole were found to be 50% - 77% sensitive amongst all the pathogens that were isolated.

4. Discussion

The study was done in four microbiology laboratories in Dhaka city with the vision of determining the antimicrobial susceptibility, including Fosfomycin against the commonest bacterial uropathogens, isolated over a three-month span (January to March 2021). In this period, out of 5389 urine specimens, 934 (17.33%) samples showed significant bacterial growth. Variations in the frequency of isolation of urinary pathogens were observed among different previous studies. The frequency is close to the incidence reported by other studies conducted in Dhaka *i.e.*, 16.8% and 16.4% [31] [32], but is higher than another Indian study who reported 4.2% UTI in a community-based study [33]. Few other studies in Dhaka city reported higher frequency of UTI *i.e.*, 27% and 24.14% respectively in hospital or clinic-based study [34] [35]. Bangladeshi populations are reluctant to visit a doctor or go for laboratory tests unless experiencing severe health complications for a particular disease condition, this attitude may cause the variations between community and hospital or clinic-based studies. In other studies, researchers reported UTI frequency, *i.e.*, 20% and 12%, respectively, in hospital or clinic-based studies [36] [37]. As this study was done in urban set up, participants had a better risk awareness and better facilities for maintaining their personal hygiene. Also factors like education, good sanitary facilities etc. contributed to our finding which shows a lower frequency of bacterial growth among study participants.

Females had a higher prevalence of UTI (73.56 percent) than males (26.44 percent) in our study, which is consistent with earlier data that suggest females have a higher frequency of UTI than males [38] [39]. 18% female and 10% of male participants had bacterial growth in our study. The close closeness of the urethral meatus to the anus, the shorter urethra, sexual intercourse, incontinence, and the inconvenience of using the toilet leads to the high prevalence of UTI in females [40] [41]. In the current study, relatively increase frequency of the UTI cases were found in the age group of less than 15 and more than 65 years which is dissimilar to reports demonstrated by some other studies [36] [42]. The high incidence of UTI at these age groups might be related to improper personal hygienic practice which includes improper toilet habit.

In this three-month period study, 95.9% of the total bacterial isolates were Gram negative bacilli while Gram positive cocci constituted only about 5%. In our study *E. coli* was the commonest cause of urinary tract infection (65.84%) followed by *Klebsiella pneumoniae* (16.49%), *Pseudomonas* spp. (6.8%), Enterobacter (5.46%), Enterococci (1.9%), *Staphylococcus aureus* (1.82%), Proteus (1.07%) and *S. saprophyticus* (0.21%) respectively. This is similar to other studies where *E. coli* was the most frequent pathogen causing UTI, as in a study conducted in Pakistan, where 62.6% cultures grew *E. coli* and in other studies also done in Pakistan, researchers found 66% and 70% *E. coli* positive culture cases [43] [44] [45]. These results were also similar with a study conducted in Karachi [46] which reflects that first two common organisms were *E. coli* and *Klebsiella pneumoniae*. Third prevalent organism in our study was Pseudomonas while in the above-mentioned study it was also Pseudomonas. In order for a successful infection and creating a satisfactory environment inside the host, strains of uropathogenic *E. coli* possess some special features that are achieved by expressing particular genes, called virulence factors. Two of the most important surface virulence factors of *E. coli* are type 1 fimbriae and P fimbriae that are crucial for the colonization process inside the urinary tract. For these reasons *E. coli* remains the predominant uropathogens in UTI.

Regarding the antibiotic sensitivity test in this study, gram negative bacteria exerted less sensitivity to the commonly used antibiotics in comparison to Gram positive bacteria, which correlates with the findings of other [47]. Among the Gram-negative isolates, the percentage of antibiotic sensitivity was as for amoxycillin/clavulanate (82.03%), meropenem (91.85%), nitrofurantoin (74.88%), cotrimoxazole (54.46%), ceftriaxone (54.35%) and ciprofloxacin (57.81%). In the present study, the overall percentage of antibiotic sensitivity for Gram-positive isolates was high for amoxycillin/clavulanate (94.73%), meropenem (92.1%), nitrofurantoin (79%), cotrimoxazole (65.78%) and ceftriaxone (65.78%) but least for ciprofloxacin (42.1%). Studies done in Bangladesh and India reported similar type of findings [48] [49]. The antibiotic resistance pattern of the bacteria causing UTIs varies from place to place and from time to time [50].

Fosfomycin gives coverage against both Gram-negative and Gram-positive bacteria like *Entererococcus* spp., *Staphylococcus aureus*, *E. coli*, *Salmonella* spp, *Shigella* spp., *Klebsiella*, *Enterobacter* sp., *Serratia* spp., *Citrobacter* spp. and *P. mirabilis* [51]. However, in our study 98.4% of *E. coli*, 55.2% *Klebsiella* spp., 78.6% *Enterobacter* spp. and 73.6 % Pseudomonas were susceptible to Fosfomycin. The most frequently identified Gram-positive uropathogen in this study was

Enterococcus fecalis (88.88%) and *Staphylococcus aureus* (100%) which were highly susceptible to fosfomycin. These findings also coincide to the findings of an Indian study [52].

When all the antibiotics were tested, maximum sensitivity was found to fosfomycin, followed by meropenem, amoxicillin/clavulanate, and nitrofurantoin for all the isolates tested. The low resistance rates detected for these antimicrobials may be attributed to less use in the empirical treatment of UTIs and may be the use of these antibiotics in hospitalized patients. Sensitivity amongst all the uropathogens for ceftriaxone, ciprofloxacin and cotrimoxazole was nearly 50% - 77%. Various studies have reported high resistance rates to these antibiotics [53] [54] [55]. Other studies have been reported similar resistance pattern to ciprofloxacin [56]. Thus, our study suggests that fosfomycin should be preferred over fluoroquinolones for use in the treatment of UTIs. By preferring fosfomycin over fluoroquinolones, they can be spared for use in other infections such as tuberculosis. It can also be seen that nitrofurantoin should be preferred over cotrimoxazole as a first-line agent for the treatment of uncomplicated UTI. Nitrofurantoin and Fosfomycin is specific for urine, resistance is quite low in almost all the isolates. Thus, these two antibiotics can be used in the treatment of UTI in outpatients sparing the other antibiotic classes (like fluoroquinolones, amoxicillin/clavulanate) for use in other illnesses.

The limitation of our study was lacking clinical information. This study was based on laboratory data only. So, we failed to provide information of UTI patients whether symptomatic or asymptomatic, complicated, or uncomplicated and distribution of patients based on the sources of infection like catheter-associated or community acquired. There were also technical limitations for the species level identification of Gram-negative bacteria.

5. Conclusion

The choice of empirical antimicrobial for UTI needs to be consistent with the antibiogram of the hospital and should be recommended based on sensitivity data. However, fosfomycin has a promising role in UTI as the level of sensitivity amongst both Gram-positive and Gram-negative uropathogens is very high. Fosfomycin represents a relatively old antibiotic, but it is not widely used in our country. So, it may be considered as a highly effective empirical oral treatment option for UTI until a urine culture analysis report is available.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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