

Original Article

Fighting Urinary Tract Infection: Fosfomycin's Efficacy against Uropathogenic *Escherichia coli* IsolatesTania Sultana¹, Md. Fakruddin², Suvamoy Datta¹, Md. Asaduzzaman Shishir¹

Abstract

Background: Urinary tract infection (UTI) is one of the major health concerns of Bangladeshi women and the increase in antibiotic resistance among the uropathogens poses a serious threat to the public health. **Objective:** To explore the sensitivity of fosfomycin, an alternative antimicrobial agent, in comparison to other antibiotics currently in use against *Escherichia coli*. **Methods:** The urine samples were inoculated on MacConkey agar medium following standard bacteriological technique and incubated overnight at 37°C. Then the plates were examined for bacterial growth and biochemical tests were performed. The efficacy of different antibiotics was assessed against the isolates by Kirby Bauer's disc diffusion method. **Results:** About 63.6% (350) of the urine samples (n= 550) were found to be culture positive. Among them, 20% of the isolates were presumed to be *Escherichia coli*, the most prevalent species, and further biochemical tests helped to confirm their identity. While considering the age group, incidence rate was higher among the young people of 21-30 years, especially women being the predominant. Resistance against different antibiotics was observed by these isolates and the highest was against Ciprofloxacin (90%) followed by Cotrimoxazole (75%), Meropenem (60%) and Amoxiclav (55%). Contrarily, the highest sensitivity was found against Fosfomycin (75%) and it could be the current drug of choice for treating UTI. **Conclusion:** Although the efficacy of Fosfomycin could be observed against the multi drug resistant (MDR) *E. coli*, continuous effort is required to generate a library of alternative antibiotics and their use should be rotated appropriately.

Keywords: Uropathogens, urinary tract infection, antibiotic resistance, efficacy, prevalence, fosfomycin

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Introduction

Urinary tract infections (UTIs) are serious public health problems which are caused by a range of pathogens and most commonly by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus*.¹ The urinary tract is the most common site of infection by *E. coli*, and more than 90% of all uncomplicated UTIs are caused by this pathogen.² *E. coli* associated UTIs are caused by uropathogenic strains of *E. coli*. The recurrence rate after a first *E. coli* infection is

44% over 12 months. Recurrent urinary tract infections have been frequently observed and analyzed nowadays, showing characteristics in the increase of microbial resistance to the antibiotics used, generating a serious threat to public health.³ Therefore, the scientific search for the effective use of antimicrobials against urinary tract infections becomes a dire necessity.⁴ Uncomplicated urinary tract infection is one of the most common indications for the use of antibiotics in the community. However, the Gram-negative organisms that can cause the infection are growing

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more resistant to the antibiotics currently in use.

Fosfomycin is an antibacterial agent, discovered back in 1969 when it was isolated for the first time during the screening of cultures in broth of a soil bacterium *Streptomyces fradiae*.⁵ This is a low molecular weight compound, which chemically belongs to the group of phosphorus epoxides and is available in two oral formulations, Fosfomycin tromethamine (or Fosfomycin trometamol) and Fosfomycin calcium.^{6,7} Primarily, this antimicrobial agent is administered orally and is partially absorbed in the small intestine.^{6,8} Fosfomycin binds to the plasma proteins insignificantly, being widely distributed in a variety of tissues through gastrointestinal absorption directly into the bloodstream, facilitated by its low molecular weight. In addition to serum, biologically relevant concentrations of Fosfomycin have been measured in the kidneys, bladder, prostate, lungs, bones and cerebrospinal fluid, as well as in inflamed tissues and abscess fluid.^{6,7,9} Fosfomycin has a broad spectrum activity, being efficient against Gram-positive and Gram-negative bacteria.¹⁰ Recent studies have also demonstrated its effectiveness *in vitro* against multi-drug resistant microorganisms, such as carbapenem resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* (extended-spectrum beta-lactamase producer) and Vancomycin resistant *Enterococcus* spp.^{6,11}

Considering the facts, the present study aimed at investigating the susceptibility of uropathogenic *E. coli* to Fosfomycin, comparing it with other antimicrobials routinely used in the treatment of uncomplicated urinary tract infections (UTI). The findings of this study will provide valuable insights for clinicians, researchers, and policymakers, aiding in the management and control of UTIs and promoting rational antibiotic use in the face of increasing antibiotic resistance.

Methods

This study was designed to assess the sensitivity of fosfomycin in comparison to amoxiclav, cotrimoxazole, ciprofloxacin and meropenem against *Escherichia coli* isolated from the urine of UTI patients. This is a quantitative and cross-sectional study carried out at the Clinical Microbiology laboratory of Department of Microbiology, Primeasia University, Dhaka, Bangladesh, between November 2020 and May 2021.

Urine samples were collected from patients

suspected of urinary tract infections (UTIs) from Islamia Bank Hospital, Dhaka and were aseptically transferred to the laboratory and processed as soon as possible. Bacterial isolation was performed by streaking the urine samples onto MacConkey agar plates. Plates were incubated at 37°C for 24 hours. Colonies showing typical morphology on MacConkey agar were selected for further analysis. Gram staining was performed to confirm the presence of gram-negative rods. Biochemical tests such as indole production, lactose fermentation, and citrate utilization were conducted to confirm the identification of *Escherichia coli*.

The Kirby-Bauer disk diffusion method was used to determine the susceptibility of *E. coli* isolates to different antibiotics. The antibiotics tested in this study were Fosfomycin, Amoxiclav (Amoxicillin + Clavulanic acid), Cotrimoxazole (Trimethoprim + Sulfamethoxazole) and Ciprofloxacin. Commercially available antibiotic disks containing specified concentrations of each antibiotic were placed on Mueller-Hinton agar plates inoculated with *E. coli* isolates. The plates were incubated at 37 °C for 24 hrs. The diameter of the zone of inhibition around each antibiotic disk was measured and interpreted based on CLSI guidelines.¹²

Results and Discussion

Antibiotic resistance is a worldwide problem and Bangladesh is a major contributor to this owing to its poor healthcare standards, along with the misuse and overuse of antibiotics. Despite being an old compound, Fosfomycin has been demonstrating, still, effectiveness *in vitro* against multidrug-resistant pathogens of the urinary tract such as carbapenem-resistant *Klebsiella pneumoniae*. Its broad spectrum activity against Gram-positive and Gram-negative bacteria is due to its early action on cell wall synthesis, making the bacteria vulnerable before it is completely formed.^{11,13}

In the present study, about 550 urine samples were collected from patients who were sick due to urinary tract infections. Of them, 63.6% (350) samples were found with the growth of uropathogens in the selective media (Figure 1a). Incidence rate was higher among the young people of 21-30 years, especially women being the predominant. Several studies indicate that the uropathogens most isolated in urinary tract infections is *E. coli*. Clinical and experimental evidence indicates that the ascent of microorganisms of enteric origin through the

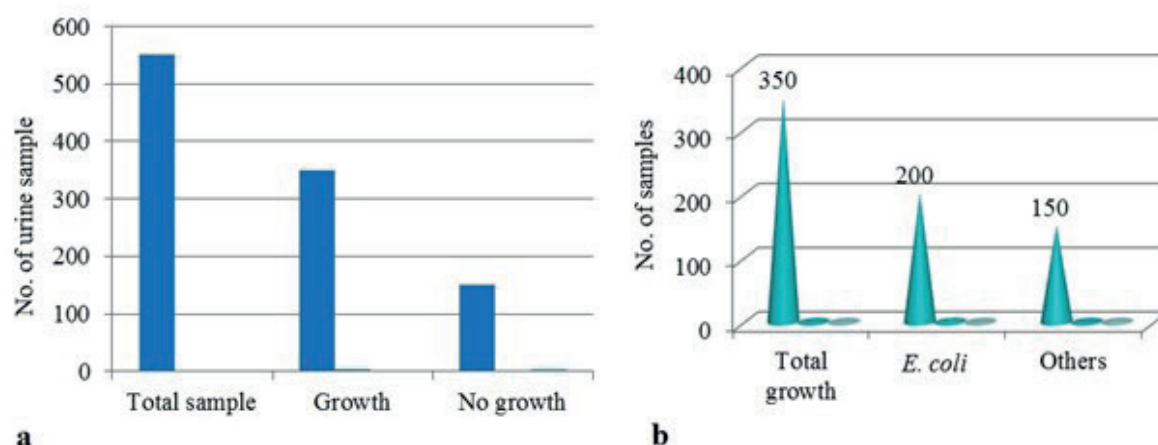


Figure 1: Prevalence of Uropathogenic *E. coli* in urine samples from patients with UTI. (a) Distribution of uropathogens in urine samples. Among the 550 urine samples, microbial growth was observed in 350 samples, indicating high prevalence of UTI in Bangladesh. (b) Prevalence of *E. coli* in patients. Among the 350 culture-positive urine samples, *E. coli* was isolated from 200 samples, indicating *E. coli* is one of the most prevalent uropathogens in Bangladesh.

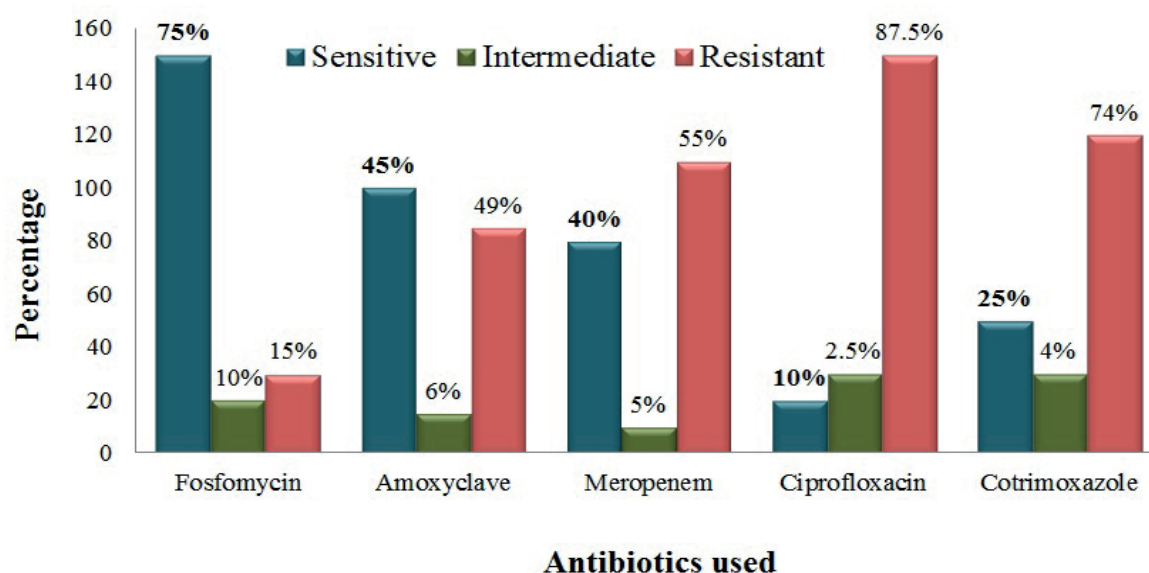


Figure 2: Sensitivity and resistance pattern of isolated *E. coli* against fosfomycin and other antibiotics. The *E. coli* isolates showed high resistance against ciprofloxacin and cotrimoxazole. Fosfomycin was found to be more effective than all the other antibiotics used in this study (namely, Amoxyclav, Meropenem, Ciprofloxacin and Cotromoxazole).

urethra, especially in women, who naturally have a shortening of this channel, promote the development of urinary tract infection (UTI).^{9,13-15} Among 350 samples, 57.14% cases (n= 200) were presumed as *Escherichia coli*, the most prevalent species, and further biochemical tests helped to confirm their identity (Figure 1b).

The antimicrobial susceptibility test was carried out for all uropathogens isolated in the present study and through comparison among the common

antimicrobials currently in used in the country for the treatment of UTI, different resistance profiles were observed. The highest resistance was against Ciprofloxacin (90%) followed by Cotrimoxazole (75%), Meropenem (60%) and Amoxiclav (55%). Based on the antibiogram test results, the highest susceptibility was found to Fosfomycin (75%) and the lowest susceptibility to Ciprofloxacin (10%) (Figure 2). It can be noted that, specifically analyzing the data referring to *E. coli*, the drug

Amoxicillin/ Clavulanate showed lower resistance rates than the general panorama of uropathogens, which predicts a safer value for use in the treatment of ITUNC. Ciprofloxacin persisted at borderline values, while Nitrofurantoin and Fosfomycin showed more optimistic values (Figure 2). It can also be inferred that, broadly analyzing the effectiveness of antimicrobials against isolated uropathogens, Nitrofurantoin and Fosfomycin had the lowest resistance rates when compared to the first choice of drugs for the treatment of ITUNC, such as Quinolones.

Quinolones are antimicrobials typically used in the treatment of UTI. In this work, this group was represented by Norfloxacin and Ciprofloxacin. Norfloxacin is considered an old quinolone indicated only in cases of ITUNC and has not demonstrated reliable results for empirical use. Therefore, Ciprofloxacin, considered modern and routinely used in the treatment of UTI, showed borderline resistance values, suggesting uncertainty regarding its efficacy in empirical treatment. The use of drugs belonging to this group may suffer from the acquisition of bacterial resistance mediated by mutations in the genes coding for subunits of DNA gyrase (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*), as well as plasmid genes such as *qnrA*, B or S and *aac(6')*-Ib-cr.^{15,16}

Nitrofurantoin, despite its slightly lower resistance values when compared to Fosfomycin, presents some difficulties regarding its pharmacological properties. Some disadvantages are observed regarding the bioavailability of Nitrofurantoin, due to the fact that it does not penetrate well into the tissues, nor does it reach systemic levels, which limits its activity to the urinary tract.¹⁴

As for Fosfomycin, it has gained therapeutic relevance in recent years mainly due to its broad spectrum of action that includes Gram-negative and Gram-positive bacteria. The effectiveness, using this drug, has also been observed against multidrug-resistant microorganisms, such as vancomycin-resistant enterococci (VRE) and extended-spectrum β -lactamase-producing enterobacteria (ESBL).^{10,15}

The high number of UTIs caused by multidrug-resistant enterobacteria of the ESBL or - AmpC-type lactamase has increased therapeutic failure with narrow-spectrum drugs. In these cases, the use of carbapenems has been the alternative

typically used by several health services. Studies focusing on Fosfomycin achieved satisfactory results for the treatment of the aforementioned multidrug resistance. This fact helps to reduce the appearance of resistance to carbapenems, which are very useful drugs in the treatment of several types of serious infections.¹⁶

The synergistic use of Fosfomycin with other drugs has also had therapeutic and preventive success with regard to the appearance of microbial resistance. Pérez et al. demonstrated in a study with strains of ESBL producing *Escherichia coli* revealed that the association between Fosfomycin and Meropenem satisfactorily reduced microbial growth rates, as well as decreased the emergence of mechanisms of resistance to Fosfomycin.⁸

The use of fosfomycin for the treatment of urinary tract infections (UTIs) caused by *Escherichia coli* has been a topic of interest in recent years. Several studies have investigated the efficacy of this antibiotic, and their findings have contributed to our understanding of its potential use in clinical practice.

In another study done by Zhanel et al. reviewed the available literature on fosfomycin and reported its effectivity in treating uncomplicated UTIs caused by *E. coli*, with a cure rate of over 80%.¹⁷ Another meta-analysis done by Falagas et al. also supported the use of fosfomycin as a first-line therapy for uncomplicated UTIs caused by *E. coli*, based on its high efficacy and low resistance rates.⁵

However, some other evidence suggested that lower efficacy rates of fosfomycin for the treatment of complicated UTIs caused by *E. coli*. As it found that fosfomycin was less effective in eradicating biofilm-forming *E. coli* strains, which are commonly associated with complicated UTIs.¹⁸

Overall, the available evidence suggests that fosfomycin can be an effective treatment option for uncomplicated UTIs caused by *E. coli*. However, its efficacy may be limited in cases of complicated UTIs caused by biofilm-forming *E. coli* strains. Therefore, its use should be carefully considered in these cases, and alternative treatment options should be explored if necessary.

However, it is important to acknowledge the limitations of our study. The analysis was limited to *E. coli* isolates obtained from urine samples, and the results may not be generalizable to other bacterial species or infection sites. Additionally,

further studies are warranted to investigate the efficacy of fosfomycin in different clinical settings and patient populations.

Our research highlights the favorable sensitivity of Fosfomycin against *E. coli* isolated from urine samples. These findings support the potential clinical utility of fosfomycin as an effective treatment option for urinary tract infections caused by *E. coli*, providing a valuable addition to the armamentarium of antibiotics. Continued research and surveillance are needed to monitor Fosfomycin's efficacy and ensure its appropriate use in clinical practice.

Conclusion

In conclusion, our study demonstrated that fosfomycin exhibited a favorable sensitivity profile, showing potent activity against the tested *E. coli* isolates. Importantly, our findings indicated that fosfomycin displayed comparable or even superior efficacy to the commonly prescribed antibiotics, including amoxyclave, cotrimaxazole, ciprofloxacin, and meropenem. This suggests that fosfomycin could serve as a promising alternative in the treatment of urinary tract infections caused by *E. coli*, particularly in cases where resistance to traditional antibiotics is encountered. While re-exploring older 'forgotten' drugs like fosfomycin

is a useful strategy, it represents only part of the multifaceted response required to tackle the complex problem of antimicrobial resistance.

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Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Ethical approval: This study was conducted in accordance with the ethical guidelines of the Institutional Ethical Approval Committee of Primeasia University, Dhaka, Bangladesh. Informed consent was obtained from all patients whose urine samples were included in the study.

Author's contribution: TF, MF, SD and MAS was involved in research concept and design, TF and MAS took part in collection and/or assembly of data, MF, SD and MAS was involved in data analysis and interpretation, MF and MAS took part in drafting the article, and SD and TF were involved in critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

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