

Fosfomycin Susceptibility in Multidrug Resistant Uropathogenic Escherichia Coli Isolates at a Tertiary Care Hospital in Jaipur, Rajasthan, India

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Abstract:

Introduction: Urinary tract infection (UTI) is one of the most common infectious diseases with the emergence of multidrug resistance (MDR) organisms. Fosfomycin has emerged as a novel oral therapeutic option.

Methods: A prospective study was conducted for 6 months in a tertiary care hospital to evaluate whether the common uropathogens were susceptible to fosfomycin. Identification of organisms causing significant bacteriuria was done by conventional biochemical testing. Antimicrobial susceptibility testing was performed against these pathogens by Kirby-Bauer disc diffusion method.

Results: A total of 200 Escherichia coli isolates were analyzed from urine culture during the study period. Among these isolates, 52% (104/200) were extended-spectrum beta-lactamases producers, 49% (98/200) were CRE and 73.5% (147/200) isolates were found to be MDR Enterobacteriaceae (MDRE). However, 95.5% (191/200) of the total isolates and 93.87% (138/147) of MDRE were found to be susceptible to fosfomycin.

Conclusion: The common uropathogens including MDR isolates show high in vitro susceptibility to fosfomycin, which therefore has the potential to emerge as a promising alternative oral agent for outpatient therapy of UTIs.

Keywords: Fosfomycin Susceptibility, Carbapenem Resistant Enterobacteriaceae, Extended-Spectrum Beta-Lactamase, Urinary Tract Infections.

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Introduction

Urinary tract infection (UTI) is a commonly encountered clinical entity both in outpatient and inpatient setting. Urinary tract infections (UTIs) are among the commonest types of bacterial infections. [1] The most common uropathogens are now harboring Multiple Drug Resistance (MDR) mechanisms against the commonly used oral antimicrobial agents for UTI caused by Gram-negative organisms, i.e., Nitrofurantoin, trimethoprim-sulfamethoxazole, fluoroquinolones and second and third-generation cephalosporins. [2]

Due to overuse and misuse of antibiotics have led to the increase antibiotic resistance in the community making most of the available oral antibiotics ineffective for use. [3] The therapy becomes difficult with the overuse and misuse of these drugs. Increased emergence of ESBL and CRE in pathogens causing UTI further makes the treatment difficult. Carbapenems remain the drug of choice in infections caused by ESBL Enterobacteriaceae; hence their consumption is increasing, which further adds to the selection and

spread of carbapenem resistance in these microorganisms. [4] Multidrug resistant (MDR) organism is bacteria which is resistant to three or more antimicrobial classes. [5] Fosfomycin tromethamine is a broad spectrum antibiotic agent as it has been approved as a single-dose treatment for acute uncomplicated cystitis. The drug has a convenient oral route of administration. It maintains high urinary concentrations for over 24 hours. [6] It inhibits synthesis of the bacterial cell wall. It is best absorbed if given before food intake and is excreted in urine. It achieves high concentration in urine of 2000 µg/ml and maintains high levels for over 24 h. [6] Hence, single-time oral therapy with fosfomycin has been recommended in uncomplicated UTI.

This study was done with the objective to determine in vitro fosfomycin susceptibility among commonly isolated uropathogens, Escherichia coli and determining the efficacy of fosfomycin against ESBL, Carbapenem resistant and MDR E.coli.

Methods

A prospective study was conducted for a period of 6 months from Dec 2021 to July 2022 in the Department of Microbiology of Sawai Man Singh Hospital, Jaipur Rajasthan, India. Urine samples were collected from patients who had clinical features suggestive of UTI from the inpatients and outpatients departments. Freshly collected mid-stream clean catch urine samples were collected from the no catheterized, alert, conscious, adult patients with indications for urine culture as assessed by the clinicians from the various departments. [7] If the patients were catheterized; then, urine samples were collected from the catheter with proper aseptic precaution with needle and syringe as described in erstwhile standard technique guidelines. [8]

Samples were collected and transferred as soon as possible. Urine samples were processed within 30 minutes of receiving samples. Direct microscopy of the uncentrifuged sample was done.

Samples were plated on blood agar and MacConkey agar by semiquantitative method and incubated at 37°C. The growth of the organism and colony count were noted. The organisms were identified by conventional biochemical testing. The antimicrobial susceptibility testing was performed by Kirby-Bauer disc diffusion method.

For detection of ESBL producers, screening was done using disc diffusion method with ceftazidime, and confirmation was done by simultaneous testing with ceftazidime and combination of clavulanate

(30/10 µg) by phenotypic confirmatory disc diffusion test (PCDDT). [9] For detection of CRE, screening was done using disc diffusion method with imipenem. [9] MDR Enterobacteriaceae (MDRE) is organisms that are resistant to any three different classes of antibiotics as defined by the guidelines. In present study, it includes resistance to any three of the following groups – cephalosporins, fluoroquinolones, aminoglycosides, folate pathway inhibitors (trimethoprim-sulfa methoxazole), and nitrofurantoin. [10]

Statistical Analysis: Data collected was compiled and entered into Microsoft Excel sheets, doubly checked for any keyboard error and percentages were used to interpret and analyses the findings.

Results

The present study included 200 isolates of E.coli, recovered from urine samples received in the Department of Microbiology, SMS Medical College, Jaipur, Rajasthan. Out of 200 isolates 90 (45%) isolates were from male patients and 110 (55%) isolates were from female patients.

Maximum isolates were from age group 21 to 30 year (30%) followed by 31 - 40 year age group (25%), 41- 50 (17.5%), 0-10 yr (10%), 11-20 (10%) 51-60 year (5%) and least were from age group >60 year (2.5%). (Figure no.1) Majority of the isolates 39.5% (79) were from inpatient departments followed by outpatient department 38.5% (77) and least from ICUs 22% (44).(Figure no.2)

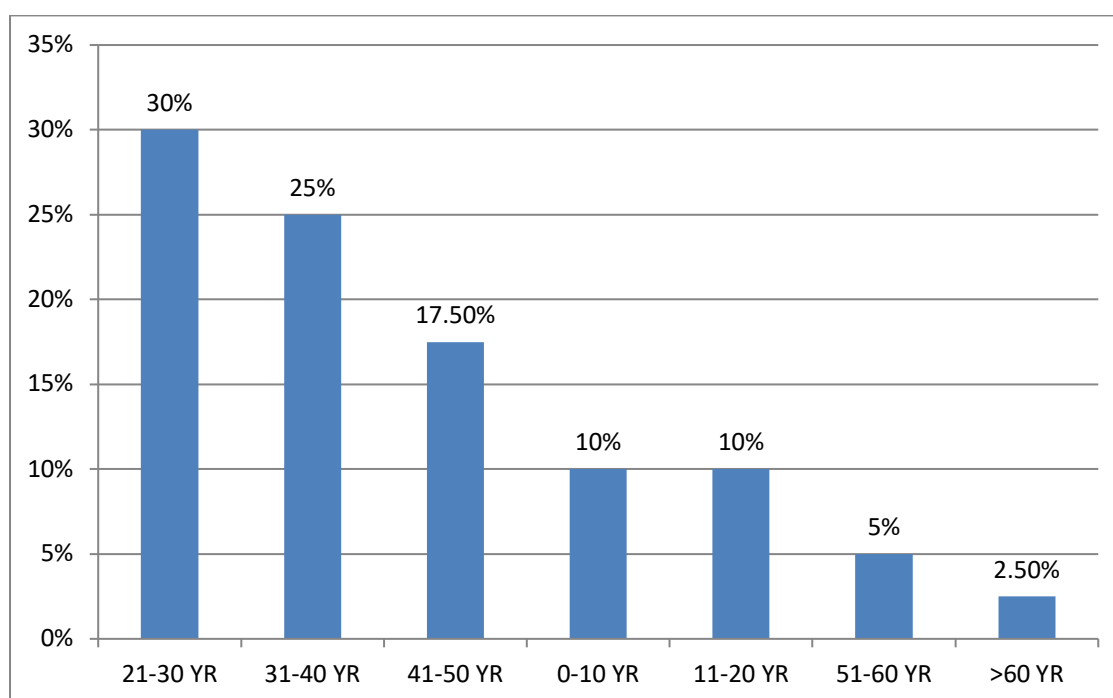


Figure 1: Distribution of E.coli strain is age group

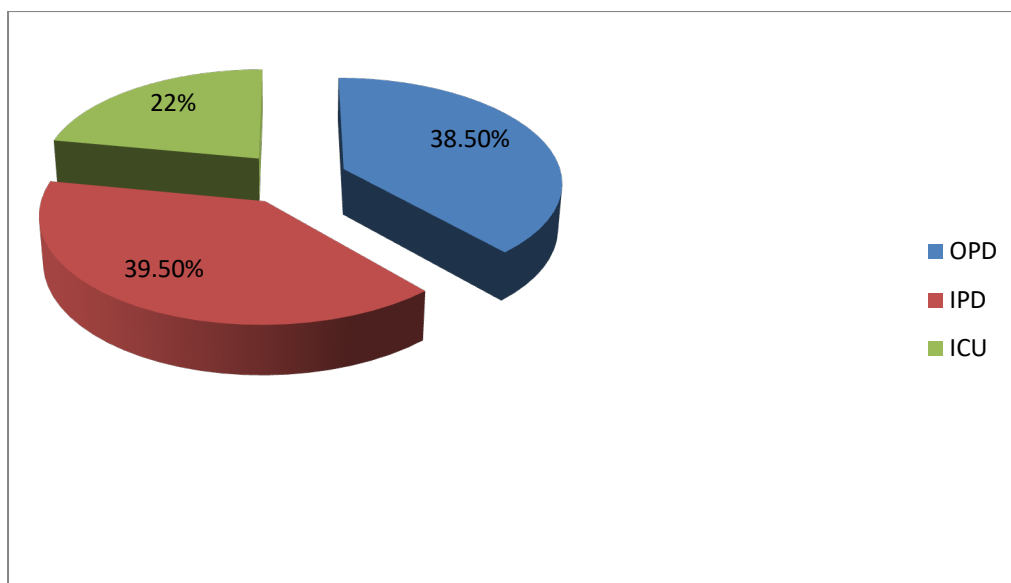


Figure 2: Ward Wise Distribution

Antimicrobial sensitivity testing showed that among the E.coli maximum isolates were sensitive to fosfomycin 95.5% (191) followed by nitrofurantoin 80% (160), imipenem 51% (102), amikacin 49% (98), ciprofloxacin 47% (94), doxycycline 43% (86), ceftazidime 32.5% (65), cefotaxime 29.5% (39) and least susceptible to ampicillin 17.5% (35). (Figure no. 3)

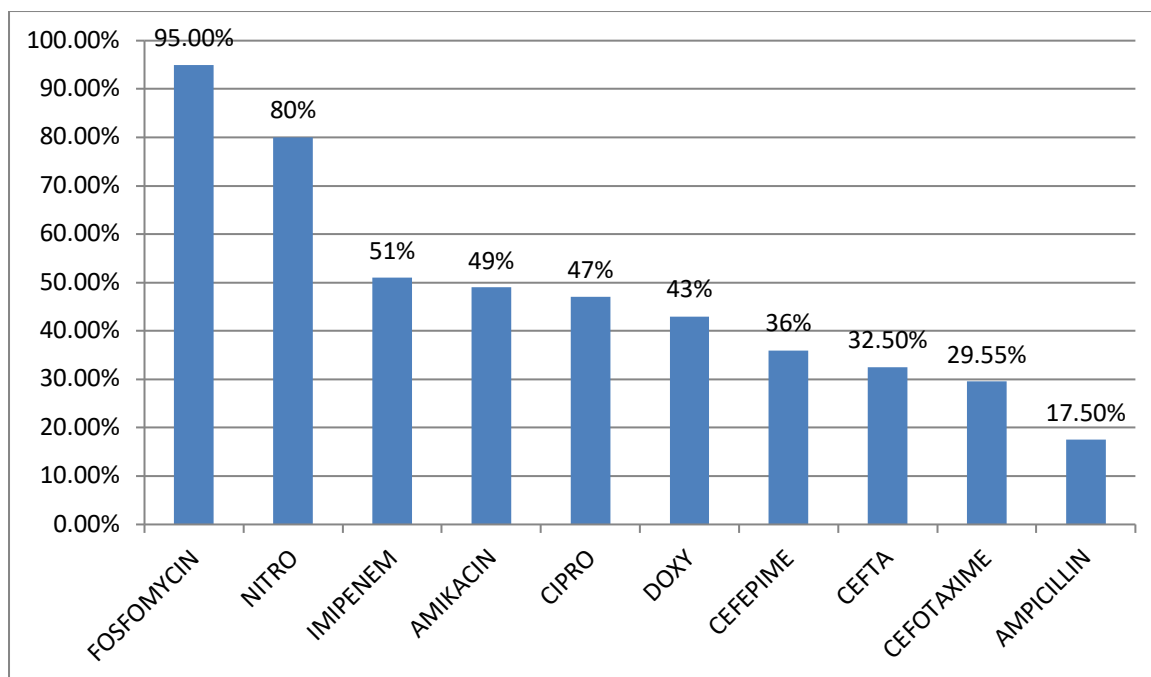


Figure 3: Antibiotic Susceptibility Pattern of E.coli isolated

Among the 200 isolates of E.coli, 67.5% (135/200) isolates were screened positive for ESBL production, out of which 77.03% (104/135) isolates were confirmed as positive by phenotypic confirmatory disc diffusion test (PCDDT). So it concludes that

overall 52% (104/200) isolates of E.coli were confirmed as ESBL producer. Out of 200 isolates 49% (98/200) were carbapenem resistant, 73.5% (147/200) isolates were found to be multi-drug resistant. (Figure no. 4)

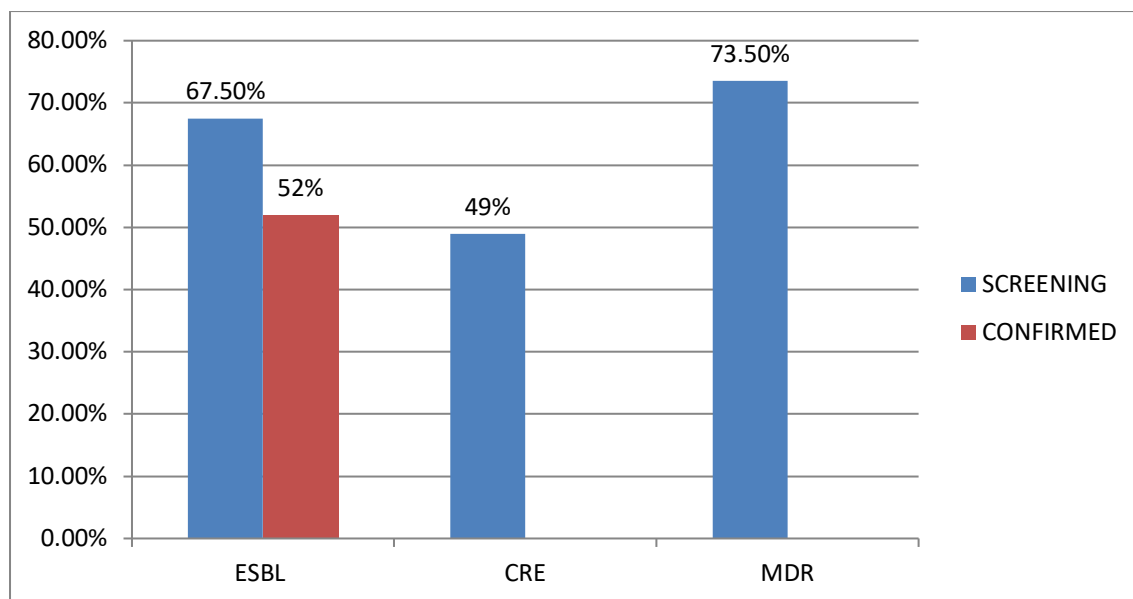


Figure 4: Different strains of E.coli

Out of 200 E.coli, 191/200 (95.5%) were fosfomycin susceptible. All ESBL producing and CRE organism were showing 100% susceptibility to fosfomycin but in case of MDR E.coli organism only 93.87% (138/147) were showing fosfomycin susceptibility. (Figure no 5)

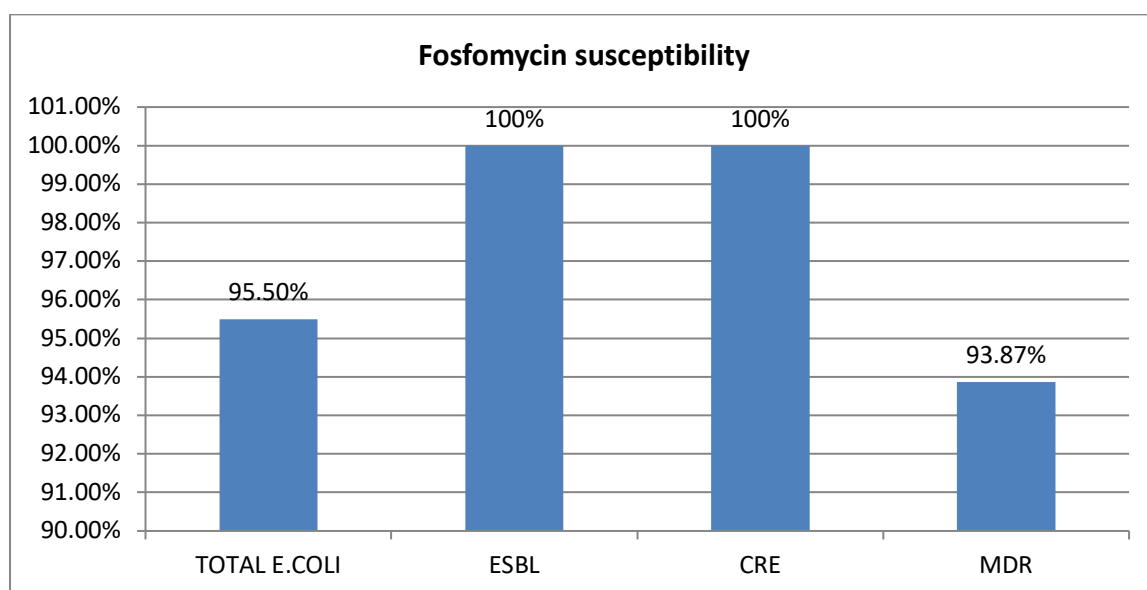


Figure 5: Fosfomycin Susceptibility Pattern

Discussion

The increasing trends of ESBL and CRE among Enterobacteriaceae isolate are creating havoc. ESBL and CRE belong to the “Critical” Priority pathogen list by WHO which are resistant to the best available antibiotics like carbapenems and 3rd generation cephalosporins for treating MDR bacteria. [11]

There is so much needed for a new drug or to review an old existing one that can be given by oral route and with low existing resistance to combat the present situation. An old broad-spectrum bactericidal agent, Fosfomycin acts by disrupting bacte-

rial cell-wall synthesis. [12] It has good invitro activity against the common uropathogens causing UTI, particularly towards the Enterobacteriaceae. [12]

The use of Fosfomycin is prevalent for UTI caused by E.coli, the most common uropathogens. [13] Recent studies have showed encouraging Fosfomycin invitro activity against MDR Gram-negative pathogens.

In cases of uncomplicated UTI, a reliable treatment modality is use of fosfomycin tromethamine, according to a study by Schito GC because of its advantages (single oral dose and a sustained high

urinary concentration) that kills bacteria rapidly and opportunity for mutant selection will decrease subsequently. Fosfomycin tromethamine has excellent tolerability and safety. [14]

Along with low resistance rates, the other benefits of fosfomycin include less cost, dosage friendly, non-toxic, non-allergic and little tendency to display cross-resistance to other antibiotics. [14]

In the present prospective study, urine samples obtained from patients diagnosed with clinical suspicion of UTI were assessed. Increasing rates of β -lactamase producing bacteria are causing serious UTI in the society and hospitals world-wide. In this study ESBL production was observed in 77.03% of E.coli isolates which is in concordance with findings in many studies from different parts of India. [15], [16]

Prevalence of carbapenamase producing E.coli isolates in the present study was 49%. Varied prevalence was observed in other studies; Shreshtha UT et al. (11.2%), [16] Mwinga MM et al (18.4%) [17]

The invitro activity of fosfomycin with other antimicrobials in ESBL producer and CR E.coli were evaluated. Amongst culture positive samples for significant bacteriuria, 104/200 (52%) isolates were found to be ESBL positive uropathogens and 98/200 (49%) were CRE pathogen which was within the range of various other studies which reported the prevalence of ESBL positive uropathogens in UTI to range from 21.8% to 64.8% [18], [19], [20]

The high sensitivity of fosfomycin in ESBL positive E.coli observed in the study was in accordance with the findings of other recent studies done by Sabharwal ER and Sharma R, (95%) and Patwardhan V and Singh S, (96.5%) [17], [21] High fosfomycin susceptibility in CRE isolates at 87.5% with 100% fosfomycin susceptibility amongst CR E.coli has been presented by other contemporary studies around the world. [19], [22], [23]

High fosfomycin susceptibility among CRE and ESBL producing isolates observed in the study further gives hope in treating these isolates causing UTI, rather than using other nephrotoxic drugs like colistin, polymyxin B which remains the only available option for treating such cases.

In the present study, 100% susceptibility was showing to fosfomycin by both ESBL producer and carbapenam resistant E.coli isolates which was in concordance with the findings of a study done by Patel B et al., in which 92% and 72.34% of ESBL positive and CRE isolates were respectively fosfomycin sensitive. [24]

Now days in the outpatient department, where oral antibiotics are preferred, minimal options are available for the oral treatment for UTI. In this study, the only available oral antibiotic with good sensitivity in ESBL positive strains other than Fosfomycin was Nitrofurantoin (80%).

Conclusion

Urinary tract infections are one of the commonest problems in health-care settings and the emergence of resistance to commonly used antibiotics has resulted in limited therapeutic options. In the majority of UTI cases, antibiotics are given empirically before bacteriology culture results are available. Fosfomycin is shown to have high in vitro activity against common uropathogens, including MDR isolates, ESBL producers, and carbapenam-resistant Enterobacteriaceae. As compared to other drugs, it has the advantage of being an oral agent with single daily dosing. It can be used in both in-and outpatient settings. Hence its use should be encouraged by clinicians. However, further studies are needed to evaluate clinical utility of fosfomycin.

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