Section: Microbiology

Original Research Article

FOSFOMYCIN SUSCEPTIBILITY PATTERN AMONG UROPATHOGENS ISOLATED FROM PATIENTS VISITING TERTIARY CARE HOSPITAL IN SOUTH INDIA BY AGAR DILUTION METHOD

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Received : 25/08/2024
Received in revised form : 12/10/2024
Accepted : 27/10/2024

Keywords:
Urinary tract infections, Fosfomycin, Agar dilution, Multi drug resistance.

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DOI: 10.47009/jamp.2024.6.5.128

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (5); 679-684

Abstract

Background: Urinary Tract Infections (UTI) are one of the most common infections encountered in clinical practice contributing for antibiotic resistance. This has limited the antibiotics options for treating the cases due to Multi Drug Resistant (MDR) bacteria. Fosfomycin is a non- traditional antibiotic which has shown promising results even against the MDR pathogens and has caught the attention of clinicians in the recent times. The objective is to determine the Fosfomycin Susceptibility pattern and Minimum Inhibitory Concentration (MIC) against Uropathogens isolated from patients visiting a tertiary care hospital in South India by Agar Dilution Method. **Materials and Methods:** This hospital based prospective study was conducted in the Department of Microbiology, Adichunchanagiri Institute of Medical Sciences, Mandya district, Karnataka, India for a period of 2 months in 2021. Non duplicate, clean catch mid-stream urine samples were collected from patients and plated on Blood Agar and MacConkey Agar. The significant growth of pathogenic bacteria was subjected to Antimicrobial Susceptibility Testing by Kirby-Bauer disc diffusion method. Fosfomycin (200 µg) disc was used and its MIC was determined by Agar Dilution Method as per Clinical and Laboratory Standards Institute (CLSI) guidelines 2021. The data was analyzed using Microsoft Excel and Statistical Package for the Social Science (SPSS). **Result:** Out of the 50 samples analyzed, E.coli (38%) was the leading isolate followed by Enterococcus spp (18%). Majority of antibiotics were reported to be resistant, whereas, Fosfomycin (90%) was recorded as the most active antibiotic against most of the uropathogens by disc diffusion method. In agar dilution method, 76% isolates were Sensitive, 16% were Intermediate and 8% were Resistant. The MIC of Fosfomycin in majority of uropathogens isolated were recorded between 8-16 µg/mL by agar dilution method. **Conclusion:** In the era of antibiotic resistance, high susceptibility with low MIC of Fosfomycin indicates that it can be used for empirical therapy in UTI patients infected with MDR isolates.

INTRODUCTION

Urinary tract infections (UTI) are one of the most commonly encountered infections in clinical practice. UTI occur in both men and women but the incidence rate in women is higher when compared to men. Nearly half of the women experience at least one episode of UTI in their lifetime with 20-40% of them experiencing recurrent episodes.[1]

E. coli is the most common organism causing UTI which accounts for up to 90% of cases followed by P. mirabilis, Klebsiella species, P. aeruginosa and Enterobacter species. Gram-positive organisms are less common which includes Group B Streptococcus, S. aureus, S. saprophyticus and S. haemolyticus.[2]

Treatment of UTIs is generally done with large proportion of broad spectrum antimicrobial agents contributing its resistance. [1,3] Increasing multidrug-resistant (MDR) pathogens contribute considerably to increasing proportion of urinary tract infections (UTIs) as they limit treatment options. [4] This has prompted re-evaluation of non-traditional antibiotics. [5] One such drug that has caught attention of clinicians in recent time is Fosfomycin. [3,6]

Fosfomycin is a bactericidal drug which acts by inactivating the enzyme phosphoenolpyruvate

ISSN (O): 2687-5365; ISSN (P): 2753-6556

synthetase, required in assembly of glycan and peptide portion of peptidoglycan, thus disrupting bacterial cell-wall synthesis. The drug therefore has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. [5,8] Advantages over newer drugs include its high urinary concentrations and minimal toxicity.

There are no much data available on the susceptibility pattern as well as MIC of Fosfomycin. Hence, the proposed study is to determine the Fosfomycin susceptibility pattern along with MIC against uropathogens by Agar Dilution Method.

Objectives: To determine the Fosfomycin Susceptibility pattern and Minimum Inhibitory Concentration against Uropathogens isolated from patients visiting a tertiary care hospital in South India by Agar Dilution Method.

MATERIALS AND METHODS

Source of data: This prospective study was conducted at department of Microbiology in a tertiary care Centre of South India for a period of 2 months in 2021. permission for this study was obtained from the Institutional ethical committee.

A total of 50 non duplicate, clean catch mid-stream urine samples were collected from patients visiting the outpatient (OPDs) and in patient department (IPD) with suspected Urinary Tract Infection(UTI) with age ≥ 16 years disregarding gender were included in the study. All the younger patients ≤16 years of age, patients with catheter and consecutive duplicate samples from same patients were excluded from the study. Samples were transported immediately to the laboratory, in case of delay >2hrs, the samples were stored at 4º-8ºC.

Direct Microscopy: Direct wet mount was prepared to observe the presence of inflammatory cells and microbial flora.

Bacterial culture: Urine samples were plated on Blood agar and MacConkey agar by standard loop method and were incubate overnight at 37ºC.

Identification of uropathogens: Urinary pathogens were identified as per standard protocol like colony morphology, Gram's stain, hanging drop preparation, Biochemical Tests-Catalase test, Cytochrome oxidase test, Nitrate reduction test, Indole test, Methyl red test (MR), voges-prausker test (VP), Triple sugar Iron agar test(TSI), Citrate utilization test, Urea hydrolysis test. For Staphylococci-Catalase test, slide and tube coagulase test. For Enterococci, Catalase test, Bile-esculin hydrolysis test, growth in 6.5%NaCl.[16]

Antimicrobial susceptibility test- The isolated organisms were further subjected to antibiotic susceptibility by Kirby-Bauer disc diffusion method as per CLSI guidelines 2021.17 E. coli ATCC 25922 and Enterococcus faecalis ATCC29212 were used as control strains. The following antibiotic discs (Hi-media Laboratory Pvt Ltd) were used –

For Gram-negative Uropathogens: Ampicillin (10µg), Amoxicillin-Clavulanate (10µg), Cefepime (30µg), Cefotoxime(30µg), Ceftriaxone(30µg), Ceftazidime(30µg), Ciprofloxacin (5µg), Levofloxacin (5µg), Ofloxacin (5 µg), Nalidixic acid (30µg), Norfloxacin(10µg), Nitrofurantoin(300µg), Chloramphenicol (30µg), Amikacin(10µg), Gentamicin (10µg), Meropenem (10µg), Imipenem(10µg), Netilmycin (30µg), Fosfomycin (200µg).

For Enterococcal isolates: Penicillin (10Units), Ampicillin (10µg), Vancomycin((30µg), Teicoplanin(30µg), Linezolid (30µg), Erythromycin (15µg), Tetracycline(30µg), Levofloxacin (5µg), Ofloxacin (5µg), Nalidixic acid (30µg), Norfloxacin(10µg), Nitrofurantoin(300µg), Chloramphenicol (30µg), Fosfomycin (200µg).

For Staphylococcus species: Penicillin (10Units), Cefoxitin(30µg), Cefotoxime(30µg), Ceftriaxone (30µg), Amikacin(10µg), Gentamicin (10µg), Ciprofloxacin (5µg), Levofloxacin (5µg), Ofloxacin (5 µg), Nalidixic acid (30µg), Norfloxacin(10µg), Nitrofurantoin(300µg), Chloramphenicol (30µg), Linezolid (30µg), Erythromycin(15µg), Tetracycline (30µg), Clindamycin(2µg), Cotrimoxazole (1.25/23.75µg), Fosfomycin (200µg).

Interpretation: Results were recorded after overnight incubation at 37°C. Zone of inhibition was measured by a ruler in millimeter and results were interpreted according to CLSI guidelines 2021. For Fosfomycin, zone diameter interpretation as per CLSI guidelines 2021.17 [Table 1].

Determination of Fosfomycin MIC by agar dilution method: Inoculum preparation and procedure- Inoculum was prepared from overnight growth on nutrient agar plate by suspending four to five morphologically similar colonies in peptone broth. After overnight incubation, the culture was diluted to contain 105 to 106 organisms per ml. This was obtained by adding 5µl of an overnight broth culture to 5 ml peptone water. Each inoculum was adjusted to 0.5 Mc Farland standards.[16]

Agar dilution was performed with Mueller-Hinton agar medium supplemented with 25 µg/ml of glucose-6-phosphate (Hi-media) to reduce the rates of false resistance. Fosfomycin trometamol was used as fosirol powder (Cipla Ltd.). Muller- Hinton agar with different concentrations of Fosfomycin (2,4,8,16,32,64,128 and 256µg/ml) was used. After adjusting the turbidity with 0.5 Mc Farland standards, 10µl of bacterial culture of test organism was spot inoculated on Muller- Hinton agar plate with different concentrations of Fosfomycin. Plates were incubated overnight at 37°C and examined for growth. E. coli ATCC 25922 and Enterococcus faecalis ATCC 29212 were used as control strains. The MIC values for testing and reporting of urinary tract isolates. [as per CLSI guidelines 2021]17 [Table 2]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

RESULTS

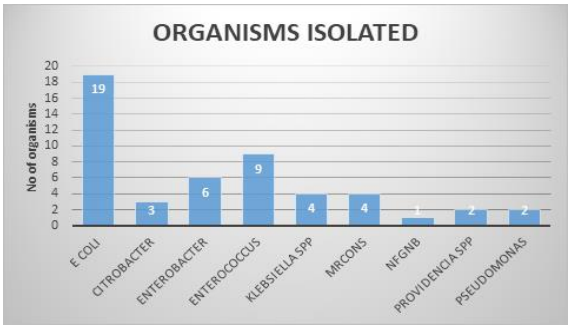

Figure 1: Organisms isolated from UTI patients

(NFGNB- Non fermenting gram negative bacilli)

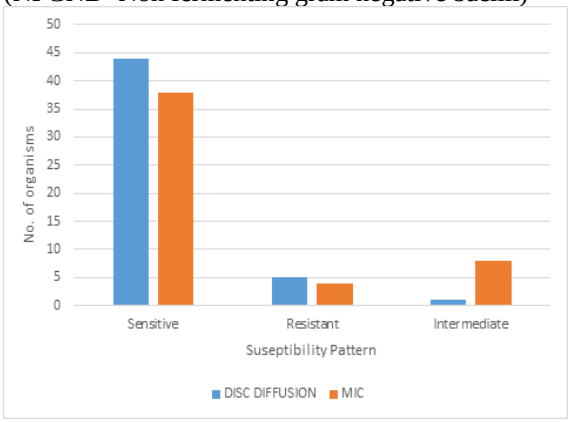

Figure 2: Comparison between Disc Diffusion & MIC of Fosfomycin

Table 1: For Fosfomycin, zone diameter interpretation as per CLSI guidelines 2021.17.

Zone diameter (mm)	Interpretation
≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant(R)

Table 2: The MIC values for testing and reporting of urinary tract isolates. [as per CLSI guidelines 2021]17

Zone diameter (mm)	Interpretation
≥64	Susceptible (S)
128	Intermediate (I)
≤256	Resistant(R)

Table 3: Age and gender wise distribution of patients.

Age	No of patients		
	Male (%)	Female (%)	Total (%)
16-30	04 (8)	09 (18)	13 (26)
31-45	01 (2)	07 (14)	08 (16)
46-60	03 (6)	05 (10)	08 (16)
>60	13 (26)	08 (16)	21 (42)
Total	21 (42)	29 (58)	50 (100)

Table 4: Organism wise antibiotic susceptibility pattern by Kirby-Bauer disc diffusion method among Gram negative uropathogens.

Organisms Antibiotics	E. coli (n=19) (%)		Enterobacter (n=06) (%)		Klebsiella (n=04) (%)		Citrobacter (n=03) (%)		Pseudomonas (n=02) (%)		Providencia (n=02) (%)		NFGNB (n=01) (%)		p-value
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	
CPM	31.58	68.42	50	50	50	50	66.67	33.33	50	50	50	50	00	100	<0.05
CAZ	21.05	78.95	66.67	33.33	25	75	66.67	33.33	50	50	50	50	00	100	<0.05
CTR	26.32	73.68	50	50	50	50	100	00	50	50	50	50	00	100	<0.05
CTX	21.05	78.95	50	50	50	50	100	00	50	50	50	50	00	100	0.14
CIP	21.05	78.95	50	50	50	50	100	00	50	50	50	50	00	100	0.15
LE	84.21	15.79	50	50	50	50	100	00	50	50	50	50	00	100	0.005
OF	73.68	26.32	50	50	50	50	100	00	50	50	100	00	00	100	0.092
NA	10.53	89.47	33.33	66.67	50	50	66.67	33.33	00	100	00	100	00	100	0.131
NX	26.32	73.68	50	50	50	50	66.67	33.33	50	50	50	50	00	100	0.358
NIT	78.95	21.05	50	50	75	25	100	00	00	100	100	00	00	100	0.05
COT	57.89	42.11	66.67	33.33	75	25	66.67	33.33	50	50	100	00	00	100	0.068
FOS	89.47	10.53	83.33	16.67	100	00	66.67	33.33	100	00	100	00	100	00	<0.05

(S-Sensitive, R-Resistant, CPM-Cefepime, CAZ-Ceftazidime, CTR-Ceftriaxone CTX-Cefotoxime, CIP-Ciprofloxacin, LE-Levofloxacin, OF-Ofloxacin, NA-Nalidixic acid, NX- Norfloxacin, NIT-Nitrofurantoin, COT-Co-trimoxazole, FOS-Fosfomycin)

Table 5: Antibiotic susceptibility pattern of Enterococcal urinary isolates

Antibiotics	Susceptibility pattern (n=9)	
	S(n) (%)	R (n) (%)
Ampicillin	05 (55.56)	04 (44.44)
Amikacin	00 (0)	09 (100)
Amoxicillin-clavulanate	05 (55.56)	04 (44.44)
Ciprofloxacin	01 (11.11)	08 (88.89)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

High level gentamycin	06 (66.67)	03 (33.33)
Linezolid	09 (100)	00 (0)
Levofloxacin	01 (11.11)	08 (88.89)
Nalidixic acid	00 (0)	09 (100)
Norfloxacin	01 (11.11)	08 (88.89)
Nitrofurantoin	08 (88.89)	01 (11.11)
Ofloxacin	01 (11.11)	08 (88.89)
Penicillin	01 (11.11)	08 (88.89)
Vancomycin	09 (100)	00 (0)
Fosfomycin	08 (88.89)	01 (11.11)

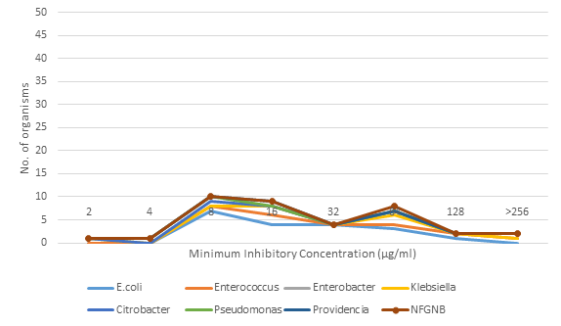

Figure 3: Fosfomycin susceptibility by MIC agar dilution among uropathogens

DISCUSSION

With the emergence of MDR, therapeutic options for treatment of UTIs are becoming limited. Fosfomycin has emerged as a novel oral therapeutic option with bactericidal activity against the MDR uropathogens. There are plenty of review literature available on usage of Fosfomycin for MDR uropathogens. but, there is no much data in correlation with clinical cases. In the era of increasing antibiotic resistance worldwide, there is a need for the revival of old antibiotics. The present study was conducted to detect the Fosfomycin Susceptibility pattern among uropathogens.

UTIs are the most prevailing ailment affecting all age groups and both genders. The most common uropathogens are showing MDR mechanisms against the commonly used oral antimicrobial agents. UTIs are emerging as treatment challenges for the clinicians. Hence, there is an urgent need to re-evaluate old antibiotics which were not much in clinical use.

In the present study females were predominant over males among UTI patients except in geriatric age group which is similar to the study of Shraddha S et al (Table 1).11Among the 50 organisms isolated from UTI patient's, majority were gram negative bacilli (74%). E. coli (38%) was found to be predominant uropathogens followed by Enterococcus (18%), which is in correlation with other studies [Figure 1].[11-16] This predominance is due to E. coli being the most common enteric flora and presence of type-1 and P fimbriae, helps it to gain entry into Urethra.[17]

Among Gram negative bacilli, the second most common uropathogens is Enterobacter (12%) followed by Klebsiella (8%) which corresponds to the other studies.3,16,18 In our study, the prevalence of non-fermenters is (2%). Similar result has been reported by other authors. [3,19]

As per the Infectious Diseases Society of America (IDSA) guidelines Co-trimoxazole is the recommended drug for the treatment of UTIs in settings where the prevalence of resistance is 20%.20 Moreover, Enterococcus species which is second most common uropathogen isolated in this study is inherently resistant to co-trimoxazole.[10] The other agents used in the treatment of UTI include fluoroquinolones, cephalosporins, other β-lactams with or without β-lactamase inhibitors and nitrofurantoin. Recently, several studies have reported increase in resistance to many commonly used antimicrobials agents. [21,22]

In this study, 42.1% and 78.9% of E. coli showed resistance to Co-trimoxazole and ciprofloxacin respectively, which is in concordance with many other studies [Table 2]. [21-24] However, Sotto a et al has reported low level resistance (26.9%) to Co-trimoxazole. [25] The overuse and misuse of Co-trimoxazole might have increased in resistance among Gram negative bacilli, in addition to this intrinsic resistant to Enterococcus has been a greater disadvantage. [10]

In present study, around 88.8% of Enterococcal isolates reported resistance to Ciprofloxacin, which is similar to the study of Mandal J et al [Table 3].[24]

In our study, Nitrofurantoin showed 78.9% and 88.8% sensitivity among E. coli and Enterococcus spp respectively, which is comparable with the study of Manjunath G N et al.26 None of the pseudomonas spp and non-fermenters were sensitive to Nitrofurantoin (Table 2). In spite of using it for long duration, Nitrofurantoin has retained its broad spectrum activity in treating UTI patients. [24]

In this study, Fosfomycin (90%) was recorded as the most active antibiotic against most of the uropathogens by disc diffusion method. 100% of sensitivity was seen in Klebsiella spp, Pseudomonas, non-fermenters and Providencia whereas, 89.47% of E. coli, 88.8% of Enterococcus spp and 83.33% of Enterobacter spp were sensitive to Fosfomycin [Table 2 & 3]. This high rate of sensitivity is reported by various studies. [11,27]

Out of 5 isolates which were resistance to Fosfomycin by disc diffusion method, only 2 isolates (E. coli, Citrobacter spp) had MIC of 128 µg/mL(Intermediate) and >256 µg/mL (Resistance) respectively. In the present study, 76% of uropathogens were reported sensitive, whereas, 16% intermediate and 8% resistance by MIC agar dilution method. Out of 50 isolates tested, 74% of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

uropathogens have MIC <32 µg/mL, 76% have <64 µg/mL (Figure 3). Although 90% of uropathogens showed sensitivity by disc diffusion method, very low MIC breakpoints were observed in agar dilution method. These findings are in correlation with other studies. [10,11,28]

CONCLUSION

There is increase in resistance against broad spectrum antibiotics such as, fluoroquinolones and co-trimoxazole drugs which are used as empirical therapy in treating UTI, hence, many studies recommend them not be used for empirical treatment. Resistance against nitrofurantoin is rare and is suitable for treatment of uncomplicated lower UTIs. High susceptibility with low MIC of Fosfomycin trometamol indicates that it can be used along with Nitrofurantoin for empirical therapy in UTI patients infected with MDR isolates.

Fosfomycin is the most active antimicrobial agent against all the uropathogens isolated in this study and in this era of antimicrobial resistance, it can be considered for the treatment of MDR UTI.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556