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Research Article

SUSCEPTIBILITY OF FOSFOMYCIN IN UNCOMPLICATED UTI: TIME TO CHANGE THE ANTIBACTERIAL PREFERENCES

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ABSTRACT

UTI is the common bacterial infectious disease in both hospital and community practice with a high rate of morbidity and economic cost associated with treatment. It has been estimated that 150 million people were infected with UTI per annum. The study is to analyze the bacteriological and antibiotic susceptibility pattern in lower UTI in a specific geographical region and to analyze the effectiveness of Fosfomycin in the treatment of lower UTI from urology outpatient department of a tertiary care hospital. Females were more prevalent for urinary tract infection and the most prevalent organism is found to be E.coli, followed by pseudomonas aeruginosa. The antibiotic sensitivity pattern of both gram negative and gram positive cocci revealed maximum sensitivity for fosfomycin (98%), followed by imipenem (79%). The study shows that uropathogens have shown decreased susceptibility to most of the available antibiotics for the treatment of UTI while fosfomycin shows high sensitivity to most of the uropathogens isolated. Our findings underline the important role of fosfomycin in the antibacterial armamentarium for the treatment of UTI. We conclude that Fosfomycin is a good alternative in the treatment of UTI.

KEYWORDS: *Fosfomycin, Uncomplicated UTI and Antibacterial.*

INTRODUCTION

UTIs encompass a spectrum of clinical entities ranging in severity from asymptomatic infection to acute pyelonephritis with sepsis. Women have more UTIs than men probably because of anatomic and physiologic differences [1]. Nearly 1 in 3 women will have had at least one episode of UTI requiring antimicrobial therapy by the age of 24 years [2]. E. coli is a frequently isolated pathogen, but it accounts for less than 50% of infections. Other frequently isolated organisms include Proteus spp., K. pneumoniae, Enterobacter spp., P. aeruginosa, staphylococci, and enterococci [3].

E. coli resistance is continuing to increase, therefore it is imperative for the healthcare professional to be familiar with the resistance trends in their geographical area when prescribing therapy [4]. Drug treatment of a lower UTI often is started before C&S results are known because the most probable infecting organism and its sensitivity to antibiotics can be predicted [5]. The choice of antimicrobial agents should preferably consider the urinalysis result, which allow for pathogen identification, in addition to antimicrobial susceptibility testing that indicates the susceptibility of microorganisms to specific group of antimicrobials [6].

The alarmingly increasing antibiotic resistance rates reported among both Gram positive and Gram negative pathogens necessitate the implementation of alternative treatment strategies. In view of the rather limited availability of novel antimicrobial agents, the re-evaluation of older antibiotic agents seems to be an appealing option. Fosfomycin, an old and rather decommissioned antibiotic, which was previously used mainly as oral (PO) treatment for uncomplicated urinary tract infections (UTIs), currently attracts clinicians' interest worldwide. Particularly, the reported activity against pathogens with advanced resistance suggests that this antibiotic may provide a useful option for the treatment of patients with these difficult-to-treat-infections [7].

METHODOLOGY

A prospective observational study was conducted at department of urology at Karuna Medical College Hospital, Palakkad, Kerala for 6 months - between from November 2017 to April 2018. Ethical approval for this study (SDAT / KMC/12-2017/84) was provided by Institutional Ethics Committee in Karuna Medical College, which permits and confirms that the institute gives approval to release the data.

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Bacterial Isolates:

The present observational study was performed on UTI cases who were referred to outpatient department of urology, Karuna medical college hospital, Palakkad from November to April .Patients those who were clinically diagnosed with UTI and those for whom urine microscopy culture and sensitivity has been ordered as a part of routine medical test were included in the study. Pediatric population of patients with UTI symptoms, patients with symptoms of acute pyelonephritis and female population on their menstrual phase, Urine specimen showing ESBL and MRSA were also excluded in the study. A total of 107 clinical isolates were obtained from the urine specimens of patients with lower UTI. Urine samples were obtained from the study subjects. UTI refers to the existence of microbial pathogens in the urinary tract and is defined as the growth of a single pathogen of > 10^5 colony-forming units per millilitre (CFU/ml) from properly collected midstream urine specimens. Proper specimen collection was instructed to all patients. All samples were processed on Muller Hinton agar using calibrated loops. The inoculated plates were aerobically incubated at 37^0C for 48 hours. The specimen was considered positive and negative for UTI if a single organism is at a concentration of ≥ 10^5 CFU/ml and < 10^2 CFU/ml respectively. Negative cultures were maintained in incubator up to 2 days. Bacterial isolates were identified on the basis of their cultural and biochemical characteristics. Identification of gram positive isolates was performed by gram staining.

Antibiotic Susceptibility Testing:

Antibacterial susceptibility of isolates was tested by Kirby-Bauer disk diffusion .For gram-negative and gram-positive bacteria, following discs were tested with their respective concentration. The following antimicrobial agents were used in the study: amikacin, ampicillin, ampicillin-sulbactam, azithromycin, cefotaxime, cefotaxime clavunalic acid, ceftazidime, ceftriaxone, cefuroxime, cotrimoxazole, doxycycline, fosfomycin, gentamycin , imipenem, levofloxacin, linezolid, meropenem, netilmycin, nitrofurantoin, norfloxacin, ofloxacin, piperacillin + tazobactam. Diameter of inhibition zones was measured after incubation at 35^0C for 18-24 hours, and data were reported as Sensitive, Intermediate and Resistant. All the collected data was analysed by the Graph pad prism version 7.0 by using one way ANOVA and p value < 0.05 was consider as statistically significant.

RESULTS AND DISCUSSION

Urinary tract infection (UTI) is the most common and a serious health affecting problem both in community and hospital settings each year worldwide. It is the second most infection after respiratory tract infection [8]. This study was conducted with an objective to analyse the bacteriological pattern in lower UTI in a specific geographical area, to study the antibacterial susceptibility pattern, and to determine the effectiveness of oral fosfomycin, thus the proper selection of an empirical antibiotic for the treatment of lower UTI. Among the total number of patients, there is a higher frequency of culture positivity in females (65%) than in males (35%). Similar studies conducted by *Rupinder Bakshi et al.,[9]* and *Razak SK et al.,* [10] which shows higher prevalence in females when compared to males.

Out of the isolated organisms, the predominant organism E.coli is mostly affected in females as compared to male followed by pseudomonas species with higher frequency in males as compared to females which correlates with the study conducted by *Ozlem Guneysel et al* [11] which states that the most common pathogen isolated from the cultures in the study group was E.coli (93.4%).

Table 1 shows that the Antibiotic sensitivity pattern of both gram negative bacilli and gram positive cocci revealed that the maximum sensitivity is for fosfomycin (98%) followed by imipenem (85.7%), nitrofurantoin (67%), meropenem (60.8%), netilmicin (59%) and cotrimoxazole (58.1%). The maximum resistance was seen against cefotaxime (62.2%), ampicillin (59.1%), cefuroxime (57.1%), norfloxacin(54.4%), ceftriaxone (54%), ceftazidime (52%) which correlates with study conducted by *A. Acharya et al.,* [12] which shows that more than 50% of common pathogens were resistant to ceftriaxone.

The antimicrobial potency and spectrum for 23 selected antimicrobial agents of different classes against the 6 most frequent gram negative UTI pathogens and 2 frequent gram positive UTI pathogens are summarized in table 2 and table 3. Among most frequently isolated gram negative and gram positive pathogens, 98% were found to be highly sensitive to fosfomycin.

E.coli showed high sensitivity to fosfomycin (97.4%) followed by imipenem (89.6%), nitrofurantoin (66.23%), Meropenem (61.03%), Cotrimoxazole (59.74%), Netilmycin (58.44). According to Supriya et al [13] susceptibility pattern showed, nitrofurantoin (62.5%), cefotaxime (58.7%), norfloxacin (44.9%), ampicillin (21.4%) and cotrimoxazole (18%).

In our study fosfomycin was found to be most sensitive followed by imipenem, nitrofurantoin, cotrimoxazole, meropenem, gentamycin, netilmycin, and doxycycline. Amoxicillin clavulanic acid, erythromycin and polymyxin is found to be least sensitive.Here, gram positive organism showed following sensitivity pattern fosfomycin in (100%), nitrofurantoin (83.3), ampicillin (50%), ofloxacin (50%), levofloxacin (50%).

Table 4 shows the comparison of efficacy of fosfomycin, nitrofurantoin, cefotaxime and Ofloxacin with respect to zone of inhibition. It was done by using Graph Pad prism with One way – ANOVA in which the p- Value was found to be extremely significant with a value of <0.0001..

On taking the reports of 75 cases out of 100 cases, the effectiveness of Fosfomycin is much more compared to other antibiotics used in the treatment of lower UTI – from the culture and sensitivity study reports. This finding is analogous with the study conducted by Smitha et al [14] that concludes fosfomycin in a single 3-4 gram dose is as effective as 7 day regimen of nitrofurantoin for the treatment of uncomplicated lower UTI in women.

Table 5 shows the zone of inhibition of Fosfomycin, Nitrofurantoin, Ofloxacin, and Cefotaxime for the 75 cases, where Nitrofurantoin, Ofloxacin and Cefotaxime are the other commonly prescribing antibiotics for lower UTI.

Table No. 1: Antibiotic sensitivity and resistance pattern of isolated organism in lower UTI

ANTIBIOTIC	S	%	I	%	R	%
AMIKACIN	37	37%	26	26%	36	36%
AMPICILLIN	21	21%	19	19%	58	58%
AMPICILLIN /SULBACTAM	41	41%	27	27%	30	30%
AZITHROMYCIN	41	41%	27	27%	30	30%
AZTREONAM	3	3%	0	0%	5	5%
CEFOTAXIME	21	21%	16	16%	61	61%
CEFOTAXIME CLAVULANIC ACID	33	33%	35	35%	24	24%
CEFTAZIDIME	33	33%	14	14%	51	51%
CEFTRIAXONE	18	18%	27	27%	53	53%
CEFUROXIME	30	30%	12	12%	56	56%
CIPROFLOXACIN	11	11%	5	5%	17	17%
COTRIMOXAZOLE	57	57%	5	5%	36	36%
DOXYCYCLINE	46	46%	21	21%	30	30%
FOSFOMYCIN	98	98%	2	2%	0	0%
GENTAMICIN	57	57%	14	14%	26	26%
IMEPENEM	79	79%	3	3%	10	10%
LEVOFLOXACIN	30	30%	22	22%	37	37%
LINEZOLID	4	4%	0	0%	1	1%
MEROPENEM	59	59%	10	10%	28	28%
POLYMIXIN	1	1%	0	0%	2	2%
NITROFURANTOIN	65	65%	12	12%	19	19%
OFLOXACIN	38	38%	13	13%	47	47%
PIPERACILLIN +TAZOBACTAM	33	33%	36	36%	24	24%
VANCOMYCIN	2	2%	0	0%	0	0%
ERYTHROMYCIN	0	0%	0	0%	1	1%
AMOXYCILLIN CLAVULANIC ACID	0	0%	0	0%	1	1%
NORFLOXACIN	27	27%	14	14%	49	49%
NETILMYCIN	56	56%	15	15%	24	24%

*n=100; *S-Sensitive; *I-Intermediate; *R-Resistant*

Table No. 2: Antibiogram pattern of most frequently isolated gram negative urinary pathogens

Antibiotics	E .coli (n=77)			Klebsiella species(n=3)			Acineto bacter (n=4)			Citrobacter (n=1)			Pseudomonas species(n=6)			Enterobacter (n=3)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Amikacin	29	21	27	0	0	3	3	1	0	1	0	0	2	2	2	1	1	1
Ampicillin	14	20	43	0	0	3	0	2	2	0	0	1	0	0	4	1	1	1
Ampicillin sulbactam	35	19	23	0	2	1	2	1	1	0	0	1	1	2	3	2	1	0
Azithromycin	18	20	36	2	0	1	0	2	2	1	0	0	3	0	2	0	2	1
Aztreonam	0	0	4	0	0	0	0	0	0	0	0	0	2	0	0	0	1	0
Cefotaxime	19	12	46	0	0	3	1	1	2	0	0	1	0	0	5	0	3	0
Cefotaxime clavulanic acid	25	8	18	0	1	0	3	1	0	0	0	1	2	0	2	0	1	0
Ceftazidime	25	12	39	0	1	2	2	1	1	0	0	1	1	0	2	3	0	0
Ceftriaxone	22	12	42	0	1	2	2	1	1	0	0	1	0	1	5	1	1	1
Cefuroxime	24	11	42	0	0	3	4	0	0	0	0	1	0	0	6	1	1	1
Cotrimoxazole	46	3	28	2	1	0	2	0	1	0	0	1	3	0	2	2	0	1
Doxycycline	36	19	22	1	0	2	3	0	0	0	1	0	1	1	4	1	0	2
Fosfomycin	75	2	0	3	0	0	4	0	0	1	0	0	6	0	0	3	0	0
Gentamycin	43	13	18	3	0	0	2	0	2	1	0	0	3	0	2	1	0	1
Imipenem	69	2	6	3	0	0	3	1	0	1	0	0	2	0	3	3	0	0
Levofloxacin	21	20	31	0	0	3	0	2	1	1	0	0	3	0	2	3	0	0
Linezolid	2	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Meropenem	47	10	20	1	0	2	3	0	1	1	0	0	2	0	3	3	0	0
Netilmicin	45	13	18	2	1	0	2	0	2	1	0	0	3	0	3	2	1	0
Nitrofurantoin	51	14	11	1	0	2	3	0	1	1	0	0	3	0	2	0	0	2
Norfloxacin	20	14	38	0	0	3	3	1	0	1	0	0	2	0	3	3	0	0

Ofloxacin	26	12	38	0	0	3	2	1	1	1	0	0	3	0	3	3	0	0
Piperacillin Tazobactam	28	29	16	0	0	3	1	2	1	1	0	0	3	1	2	0	1	0

**S-Sensitive; *I-Intermediate; *R-Resistant*

Table No. 3: Antibiogram pattern of most frequently isolated gram positive urinary pathogens

Antibiotics	Enterococcus species (n=4)			Coagulase negative staphylococcus (n=2)		
	S	I	R	S	I	R
Amikacin	0	2	2	1	0	0
Ampicillin	3	0	1	0	0	0
Ampicillin sulbactam	2	1	1	0	0	0
Azithromycin	2	1	0	0	0	0
Aztreonam	0	0	1	0	0	0
Cefotaxime	2	1	1	0	0	0
Cefotaxime clavulanic acid	3	0	0	0	0	0
Ceftazidime	2	0	2	0	0	1
Ceftriaxone	2	1	1	0	0	0
Cefuroxime	1	0	3	0	0	0
Cotrimoxazole	1	0	3	1	0	0
Doxycycline	2	1	1	0	0	0
Fosfomycin	4	0	0	2	0	0
Gentamycin	2	1	1	0	0	0
Imipenem	3	0	1	0	0	0
Levofloxacin	3	0	0	0	0	0
Linezolid	1	0	0	2	0	0
Meropenem	2	0	2	0	0	0
Netilmicin	1	1	2	0	0	0
Nitrofurantoin	4	0	0	1	0	0
Norfloxacin	1	0	2	0	0	0
Ofloxacin	2	0	2	1	0	0
Piperacillin Tazobactam	1	2	1	0	0	1

**S-Sensitive *I-Intermediate *R-Resistant*

Table No. 4: Comparison of the efficacy of fosfomycin with other commonly prescribed antibiotics with respect to the zone of inhibition

SL. No	Fosfomycin ZOI	Nitrofurantoin ZOI	Cefotaxime ZOI	Ofloxacin ZOI
1	S	S	R	I
2	S	S	S	R
3	S	R	S	R
4	S	S	R	R
5	S	S	R	R
6	S	S	R	R
7	S	R	R	S
8	S	R	R	S
9	S	R	R	S
10	S	S	S	S
11	S	R	R	I
12	S	S	R	R
13	S	I	R	R
14	S	S	R	S
15	S	I	S	S
16	S	S	S	S
17	S	S	I	S
18	S	S	I	R
19	S	S	R	R
20	S	S	R	R
21	S	I	R	R

22	S	S	S	R
23	S	R	R	S
24	S	R	S	S
25	S	S	S	S
26	S	S	R	S
27	S	S	S	S
28	S	S	R	R
29	S	S	R	R
30	S	S	R	R
31	S	S	R	R
32	S	R	R	R
33	S	S	R	R
34	S	I	S	I
35	S	S	S	I
36	S	S	R	R
37	S	S	I	R
38	S	S	I	R
39	S	I	R	S
40	S	I	I	S
41	S	S	R	R
42	S	S	R	S
43	S	S	S	S
44	S	S	R	R
45	S	S	R	R
46	S	S	S	R
47	S	S	R	R
48	S	R	I	R
49	S	S	S	S
50	S	S	R	R
51	S	S	R	R
52	S	S	I	S
53	S	S	R	R
54	S	S	I	S
55	S	S	I	I
56	S	R	R	R
57	S	S	I	S
58	S	S	R	S
59	S	I	S	S
60	S	I	R	R
61	S	S	I	S
62	S	S	S	S
63	S	R	R	I
64	S	S	R	I
65	S	S	R	R
66	S	I	R	R
67	S	S	R	S
68	S	I	R	S
69	S	S	I	S
70	S	S	R	R
71	S	S	R	R
72	S	S	R	I
73	S	S	R	R
74	S	S	I	S
75	S	I	R	S

Manufacturer's provided ZOI (mm)	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**
	≥16	13-15	≤12	≥17	15-16	≤14	≥23	15-22	≤14	≥16	13-15	≤12

S – Sensitive; ***I – Intermediate;*** ***R – Resistant***

Table No. 5: Comparison of the statistical parameters of the Antibiotics

Antibiotics	Mean	Standard Deviation	Standard Error of Mean
Fosfomycin	29.96	3.54	**0.3909**
Nitrofurantoin	17.85	4.104	**0.4532**
Ofloxacin	13.46	5.84	**0.6449**
Cefotaxime	**12.95**	**7.501**	**0.8284**

Table No. 6: Comparison of the efficacy of Antibiotics with respect to Fosfomycin

COMPARISON TEST	SIGNIFICANCE	P VALUE
FOSFOMYCIN vs. NITROFURANTOIN	****	<0.0001
FOSFOMYCIN vs. CEFOTAXIME	****	<0.0001
FOSFOMYCIN vs. OFLOXACIN	****	<0.0001

It shows the comparison of the statistical parameters such as mean, median, standard deviation and standard error. These statistical parameters are obtained from graph pad prism version 7.0 using one way ANOVA method. The figure shows the comparison of the effectiveness of Fosfomycin with Nitrofurantoin, Ofloxacin, and Cefotaxime. It reveals that fosfomycin is more effective as compared to other commonly prescribed antibiotics followed by Nitrofurantoin. It shows a statistically significant value of $p<0.0001$. In the management of uncomplicated UTIs, Fosfomycin should be included in empirical treatment. This finding is analogous with the study conducted by Ozlem Guneysel et al. [15].

CONCLUSION

It is concluded that gram negative bacilli (E. coli) were responsible for majority of urinary tract infections and most of the strains are multidrug resistant. The drug resistance among uropathogens is an evolving process, therefore routine surveillance and clinical trials should be done regularly with the assistance of treating physicians to reach the most effective empirical treatment.

Our findings underline the important role of fosfomycin in the antibacterial armamentarium for the treatment of UTI. Therefore a single dose of fosfomycin has higher efficacy and better compliance over other commonly prescribed drugs like (ofloxacin, nitrofurantoin) making it a first choice for uncomplicated lower UTI.

We conclude that Fosfomycin is a good alternative in the treatment of UTI. Educating patients regarding the potential for resistance to the drug they are being prescribed and need for re-evaluation and urine culture if symptoms do not improve are also important. High rate of multidrug resistance was recorded among all isolates.

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