Int.J.Curr.Microbiol.App.Sci (2023) *12*(04): 135-141

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 12 Number 4 (2023)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2023.1204.015

To Study Activity of Fosfomycin Against Extended Spectrum Beta- Lactamases in Uropathogens in a Tertiary Level Maternity Hospital of Western Rajasthan

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Keywords

UTI, GNB, GPC, AST, ESBL, Fosfomycin, fluoroquinolones, cephalosporins

Article Info

Received: 10 March 2023
Accepted: 04 April 2023
Available Online: 10 April 2023

A B S T R A C T

Urinary tract infections are the most important healthcare complications experienced in medicine and urology. Unfortunately, besides B-lactams, the Extended spectrum beta lactam producing Gram negative uropthogens causing UTI have become associated with resistance to other antibiotics such as aminoglycosides, fluoroquinolones etc. The use of old antibiotic such as Fosfomycin been introduced again in the field of therapeutic. The present study was conducted prospectively in the Department of Microbiology, Jodhpur, Rajasthan. Over a period of 6 months. Mid-stream morning urine samples were collected aseptically. Semi quantitative culture was done on UTI HICROME Agar. Results: In present study time 2000 (40.97%) urine sample were received, out of which 1511 (75.55%) were culture positive, 300 (15%) were sterile and 189 (9.45%) were insignificant bacterial count, Gram negative bacilli were 1100 (72.79%), Gram positive cocci were 411 (27.200%). Among GNB isolates *Escherichia coli* 501 (45.54%) was the most common isolate followed by *Klebseilla* spp.189 (17.18%), *Citrobacter* spp. were 130(11.81%), *Pseudomonas* spp.120 (10.90%), *Aceinatobacter* spp.110 (10%) and *Proteus* spp. were 50 (4.54%). Age-wise distribution 20-29 years (60.36%) group was the most common. Fosfomycin was the most sensitive antibiotic was reported. The culture and Antibiotic sensitivity testing (AST) of uropathogens should be done. Fosfomycin found to be suggesting that it could be used as empiric monotherapy for uncomplicated UTIs.

Introduction

Urinary tract infections [UTIs] are the most important healthcare complications experienced in medicine and urology. UTIs bring great stiffness and reduce significantly the standard of life. UTIs rank second after respiratory tract infections in outpatient department (Hareendranath *et al.*, 2021). The most common uropathogens are *Escherichia coli*, *Klebsiella* spp. and *Enterococcus* spp. etc. Symptomatic uncomplicated UTIs being empirically treated in clinical practice. Unfortunately, besides B-lactams, the Extended spectrum beta lactam [ESBL] producing Gram negative uropthogens causing UTI have become associated with resistance to other antibiotics such as aminoglycosides, fluoroquinolones, cephalosporins but they do not affect cephamycins (e.g. cefoxitin or cefmetazole) developing multi-drug resistance [MDR]. The problem of MDR uropathogens contribute considerably to hike the cases of UTIs.

Due to limited therapeutic antibiotics. The use of old antibiotic such as Fosfomycin (first isolated in Spain in 1969) have been introduced again in the field of therapeutic. Fosfomycin trometamol is a well-tolerated drug as well as have a broad spectrum of activity against a wide range of Gram negative as well as Gram positive bacteria (Al-Quraini *et al.*, 2022). It is a bactericidal antibiotic, inhibits the cell wall formation and antibiotics cross-resistance has been uncommon. It is now a first-line treatment option for uncomplicated UTIs in women in many countries (Rodríguez-Baño and Pascual, 2008).

Materials and Methods

The present study was conducted prospectively in the Department of Microbiology, Umaid hospital, Jodhpur, Rajasthan. Over a period from January 2022 to July 2022. Mid-stream, morning urine samples were collected aseptically in sterile universal containers.

The samples were received in Microbiology lab, semi quantitative culture was done on UTI HICROME Agar (a chromogenic agar). After an aerobic incubation at 37°C, the plates showing significant growth as per the Kass count (single species count of more than 10^5 organisms per ml of urine) were processed further and the isolates were identified according to standard Text Book of Microbiology (Collee *et al.*, 1996).

All Gram negative bacteria tested for ESBL production were included in the present study. Antibiotic sensitivity testing was done by the Kirby Bauer disc diffusion method as per CLSI guidelines (CLSI, 2017). The following antibiotic discs (drug concentration μg) were used: Amoxicillin (20), Cefuroxime (30), Ceftazidime (30), Ceftazidime/clavulanic acid (30/10), Cefepime (30), Ciprofloxacin (5), Amikacin (30), Nitrofurantoin (300), Imipenem (10), fosfomycin (200).

Double Disc Diffusion Test for ESBL Detection

Single disc of Ceftazidime (30mcg) and a combination of clavulanic acid (10 mcg) and ceftazidime (30 mcg) disc was used. Both discs were placed on Muller Hinton agar plates which were earlier swabbed by respective culture and incubated for 24 hrs. At 37°C. More than 5mm increase in the zone diameter for Ceftazidime- Clavulanic acid was considered positive ESBL production (CLSI, 2017).

Results and Discussion

In present study time total 4881samples were received for culture and sensitivity test, out of which 2000 (40.97%) were urine sample, out of which 1511 (75.55%) were culture positive, 300 (15%) were sterile and 189(9.45%) were insignificant bacterial count, Gram negative bacilli were 1100 (72.79%), Gram positive cocci were 411 (27.200%). Amongst GNB isolates *Escherichia coli* 501 (45.54%) were the most common isolates followed by *Klebseilla* spp.189 (17.18%), *Citrobacter* spp. were 130(11.81%), *Pseudomonas* spp.120(10.90%), *Aceinatobacter* spp.110(10%) and *Proteus* spp. were 50(4.54%).

The expandation of extended-spectrum β-lactamases (ESBLs) from health-care settings as well as from community is quite alarming. DDST for ESBL enzymes is a good epidemiological tool to assess the overall situation in a certain setup. Good hand hygeine can reduce the spread of ESBL. Prolong hospitalization can be avoided wherever possible. As early as possible remove catheter/needles and other prosthetics to avoid formation of biofilm. There should be appropriate hospital antibiotics policy to avoid overuse and misuse of antibiotics (Murray *et al.*, 2021). There should be infection control policy. Educate hospital staff against danger of cross infection. The knowledge of the resistance pattern of bacterial strains in a geographical area will help to guide the appropriate antibiotic use and such institutional studies will help to formulate an empirical antibiotic policy to treat Gram negative infections.

While options like, β-lactam/β-lactamase inhibitor combinations and carbapenem exist, they are blemish by various factors like parenteral use and, there by conflicting their role in the outdoor patients. There is need for a newer antimicrobial agent that is orally active, which also shows lesser resistance pattern. Fosfomycin is an old broad-spectrum bactericidal antimicrobial agent that acts by inactivating the enzyme phosphoenolpyruvate synthetase, required in assembly of glycan and peptide portion of peptidoglycan, thus disrupting bacterial cell-wall synthesis (Anand *et al.,* 2019).

Due to its improved pharmacokinetics Fosfomycin is reassure for use in UTIs; the mean peak urinary concentration of an oral single dose of 3 g fosfomycin tromethamine occurs within 4 hour, while concentrations sufficient to inhibit the majority of the uropathogens can be maintained for 1 to 2 days.

In present study *Escherichia coli* 501 (45.54%) was the most common uropathogen isolated followed by *Klebseilla* spp.189 (17.18%).Similar study done by Sood *et al.,* (2012) in their study most common pathogen was *Escherichia coli.* (17.19%) because Enterobacteriaceae have several factors responsible for their attachment to the uroepithelium. These gram negative aerobic bacteria colonize the urogenital mucosa with adhesion, pili, fimbriae, and P1-blood group phenotype receptor. In age-wise distribution analysis shows that most common age group was 20-29 (60.36%) this is similar to study done by Sood *et al.,* (2012) their prevalence rate was 69% in reproductive age group incidence of symptomatic UTI is high, and the risk is strongly associated with recent sexual intercourse, recent use of diaphragm with spermicide etc.

In present study sensitivity pattern showed that Fosfomycin was the most sensitive drug followed by Nitrofurantoin. Fosfomycin was found to be susceptible in 99.60%, 98.41% in *Escherichia coli, Klebsiella* spp respectively. These data are in concordance with others (Batra *et al.,* 2020; Banerjee *et al.,* 2017; Rajeshwari, 2021)

The culture and antibiotic susceptibility testing of uropathogens should be done. Among the oral antibiotics, most efficacious showing least resistance antibiotic is Fosfomycin. Fosfomycin was found to be suggesting that it could be used as empiric monotherapy for uncomplicated UTIs.

While, previously used antibiotics (cotrimoxazole, nitrofurantoin) have failed to cure the infection or when the patients are intolerant to the first-line treatment.

Table.1 Age-wise distribution of isolates

S.No.	Age	N(%)
1	< 20	130 (11.81%)
2	20-29	664 (60.36%)
3	30-39	180(16.36%)
4	>40	126 (11.45%)
5	Total	1100 (55%)

Table.2

S.No	Isolates	Total	%
1	**GNB (1100)**		
a)	*Escherichia coli*	501	45.54%
b)	*Klebsiella* spp	189	17.18%
c)	*Citrobacter* spp	130	11.81%
d)	*Pseudomonas* spp	120	10.90%
e)	*Acientobacter* spp	110	10%
f)	*Proteus* spp	50	4.54%
2	GPC		
a)	CONS	242	58.88%
b)	*Enterococcus* spp.	158	38.44%
c)	*S.aureus*	11	2.67%
3	Insignificant count	189	9.45 %
4	No aerobic count	300	15 %

Table.3 ESBL producer and Non ESBL producer.

S.No	Isolates	ESBL producer	Non ESBL producer
1	*Escherichia coli*	296(59.08%)	205(40.91%)
2	*Klebsiella* spp.	115(60.84%)	74(39.15%)
3	*Citrobacter* spp.	18(13.84%)	112(86.15%)
4	*Pseudomonas* spp.	98(81.66%)	22(18.33%)
5	*Acinetobacter* spp.	28(25.45%)	82(74.54%)
6	*Proteus* spp.	10(20%)	40(80%)

Fig.1

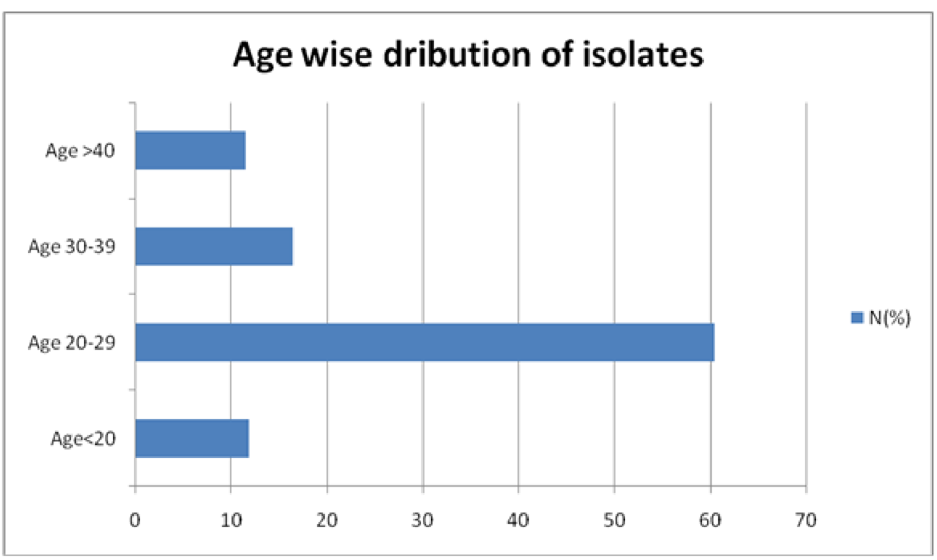


Table.4 Sensitivity pattern of isolates.

S.No	Isolates	AMC	CFR	CAZ	CAC	CPM	AT	CIP	AK	NIT	FO
1	*Escherichia coli*	9 (1.79%)	12 (2.39%)	44 (8.78)	205 (40.91%)	210(41.91%)	338(67.46%)	170(33.93%)	233(46.50%)	401(80.03%)	185(99.60%)
2	*Klebsiella* spp.	11(5.82%0	1(5.29%)	120(63.49%)	74(39.15%)	118(62.43%)	142(75.13%)	114(60.31%)	114(60.31%)	170(89.94%)	186(98.41%)
3	*Citrobacter* spp.	15 (11.53%)	25 (19.23%)	20 (15.38%)	112(86.15%)	128(98.46%)	98(75.38%)	115(88.46%)	103(79.23%)	120(92.30%)	128(98.46%)
4	*Pseudomonas* spp.	9(7.5%)	8(6.66%)	10(8.33%)	22(18.33%)	114(95%)	110(9%)	112(93.33%)	98(84.66%)	102(85%)	116(96.66%)
5	*Acienatobacter* spp.	2(1.81%)	9(8.18%)	10(9.09%)	82(74.54%)	10(9.09)	189(80.90%)	10(9.09%)	27(24.51%)	91(82.72%)	102(92.72%)
6	*Proteus* spp.	14(28%)	32 (64%)	40 (80%)	40(80%)	33(66%)	32(64%)	42(84%)	42(84%)	48(96%)	50(100%)

Fig.2

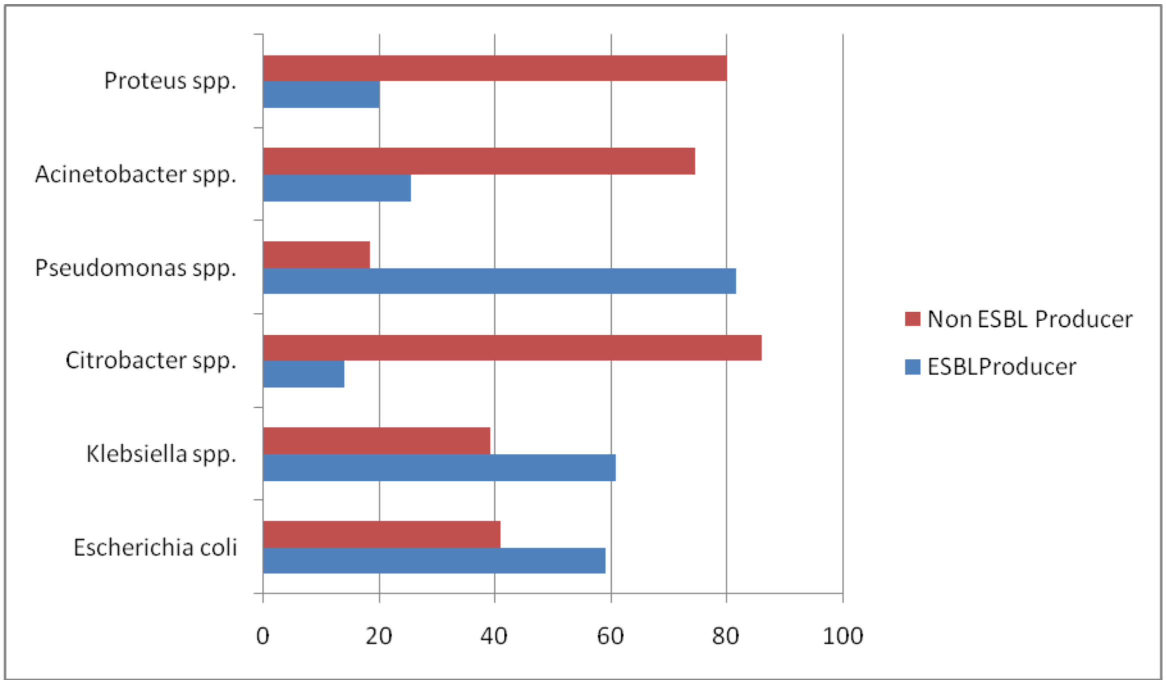
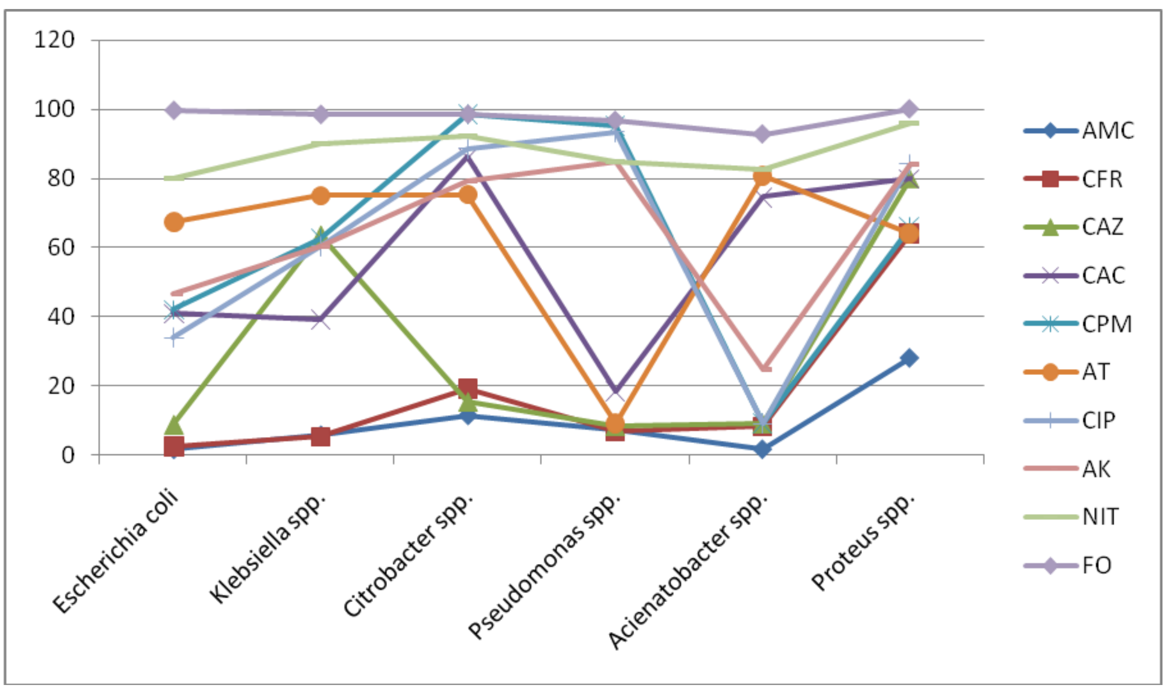

Proteus spp.
Acinetobacter spp.
Pseudomonas spp.
Citrobacter spp.
Klebsiella spp.
Escherichia coli
0
20
40
60
80
100
Non ESBL Producer
ESBLProducer

Fig.3


120
100
80
60
40
20
0
Escherichia coli
Klebsiella spp.
Citrobacter spp.
Pseudomonas spp.
Acienatobacter spp.
Proteus spp.
AMC
CFR
CAZ
CAC
CPM
AT
CIP
AK
NIT
FO

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How to cite this article:

Vishakha Ashopa, Ekta Gupta, Eshank Gupta, Anjali Beelwal and Prabhu Prakash. 2023. To Study Activity of Fosfomycin Against Extended Spectrum Beta- Lactamases in Uropathogens in a Tertiary Level Maternity Hospital of Western Rajasthan. *Int.J.Curr.Microbiol.App.Sci.* 12(04): 135-141.

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