



**IN VITRO ACTIVITY OF FOSFOMYCIN AND NITROFURANTOIN AGAINST UROPATHOGENS FROM URINARY TRACT INFECTION IN A TERTIARY CARE HOSPITAL IN SOUTH BIHAR**

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**ABSTRACT**

**Introduction:** Antibiotic resistance in Uropathogens is a worldwide problem. With the evolution and modernisation, medical practice in India is facing strong challenges by development of drug resistance in bacteria. With no development of newer antibiotics, physicians are evaluating whether older antimicrobials are again becoming useful. Thus, Fosfomycin and Nitrofurantoin are gaining attention as they are showing good response in treatment of urinary tract infection.

**Aims:** To evaluate the various Uropathogens causing UTI & their invitro susceptibility to Nitrofurantoin & Fosfomycin in patients attending hospital. **Materials and Methods:** This prospective study was conducted in Department of microbiology, Narayan medical college & hospital, Sasaram from November 2018 to June 2019. A total of 1110 samples were processed, 271 sample showed pure growth of various isolate. Antibiotic sensitivity testing was done by Kirby-Bauer disc diffusion testing and interpretation was done according to the CLSI guidelines 2018 (M100-S23).

**Results:** 271(24.4%) cases showed positive growth in 1110 urine samples. The predominant isolates were E. coli (no=142), klebsiella spp. (no=31), p. aeruginosa (No=32) among gram negative bacteria, staphylococcus spp. (no 40) and Entrococcus spp. (no =15) among gram positive bacteria.

**Conclusion:** In the era of increasing drug resistance older antibiotics like Fosfomycin & Nitrofurantoin can prove to be a good first line empirical option to treat UTI.

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**INTRODUCTION**

Urinary tract infection (UTI) is one of most common infection affecting people attending outdoor & inpatient department of hospital. With the unregularized and ill-monitored use of antibiotic prescribing pattern of treatment protocol, we are currently facing the menace of antibiotic resistance. So, the very common antibiotics in our treatment protocol are increasingly becoming useless and burden to health of patient. With the further advancement in medical science & technology, still, No or few antibiotics has been recently discovered. With the increasing resistance, clinicians have no other option rather to resort to advance, costly and reserve antibiotics to treat UTI. Another, strategy is look towards older antibiotics, whether they have still useful or how much affected by increasing resistance amongst common bacterial isolates of UTI. Nitrofurantoin and Fosfomycin are one of the most much talk about antibiotics increasingly prescribed in people affecting UTI.

Fosfomycin was first isolated in Spain in 1969 & is available as an oral formulation that can be given as a single dose (3gm sachet).

In many countries it is now a first-line treatment option for uncomplicated urinary tract infection in women [1]. This single-dose regimen is attractive due to better adherence and is generally well tolerated. Nitrofurantoin has been available since 1953. Nitrofurantoin get reduced by bacterial enzymes producing 'highly reactive electrophilic' metabolites, results in inhibition of protein synthesis by interfering bacterial ribosomal proteins [2]. Nitrofurantoin has good oral bioavailability (80%) and approximately 25% is excreted unchanged in the urine[3]. Therapeutic concentrations of Nitrofurantoin are exclusively available in the urinary tract[4], so the clinical use of nitrofurantoin is specific for the treatment of uncomplicated urinary tract infection. The aim of this study was to assess the in vitro activity of fosfomycin and Nitrofurantoin against Uropathogens from Urinary Tract Infection in a Tertiary Care Hospital.

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**MATERIALS AND METHODS**

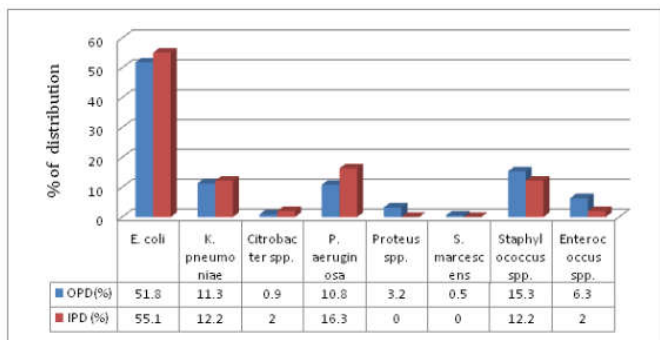
This prospective study was conducted in Department of microbiology, Narayan medical college & hospital; Jamuhar, Bihar from November 2018 to June 2019 after institutional ethical committee clearance. A total of 1110 urine samples were processed and Patients were instructed to provide freshly passed midstream ‘clean catch’ urine. From catheterized patients, urine sample were collected following standard guidelines. Urine sample were processed within 30 minutes of collection. Urine sample were processed only those patient who had history of no prior antibiotic therapy. Microscopy of uncentrifused urine had been done to note pus cells & other bacteria.

Urine samples were inoculated on CLED agar followed by identification and speciation by Kirby-Bauer disc diffusion method as per CLSI guidelines 2018 (M100-S23) [5]. The antimicrobials applied in this study are fosfomycin-FO(200µg), nitrofurantoin-NIT (300µg), amoxyclav-AMC(20/10µg), co-trimoxazole-COT(25µg), ceftriaxone-CTR(30µg), cefoxitin-CX (30µg), ceftriaxone/sulbactam-C/S(75/30µg), cefixime-CFM (5µg), amikacin-AK(30µg), ciprofloxacin-CIP (5µg), Meropenem-MRP(10µg), imipenem-IMP(10µg), levofloxacin-LE(5µg), gentamicin-GEN(10µg), piperacillin/tazobactam-PIT (100/10µg). American Type Culture Collection (ATCC) *E. coli* (25922), *Klebsiella pneumonia* (70603), *proteus vulgaris* (49132), *pseudomonas aeruginosa* (27853) were used as control strains.

All the datas including patient profiles, isolates and antimicrobial sensitivity pattern were analysed using MS office Excel worksheet. Descriptive and inferential statistics were applied (percentage and Z test). The values of *p* were kept significant at the < 0.05.

**RESULT**

This study revealed that 24.4% cases showed positive growth. Total numbers of positive cases included 140 (51.7%) males while female were 131(48.3%). On age wise analysis, the number of female patients (67%) outnumbered male (33%) in 20-39 yrs age group, while in patient ≥ 60 yrs age group, number of male patient were high in comparison to female. In patient, age-group ≤ 19 yrs male & female were almost similar. The maximum numbers of cases were from outdoor department (81.9%) in comparison to in-patient department (18.1%).

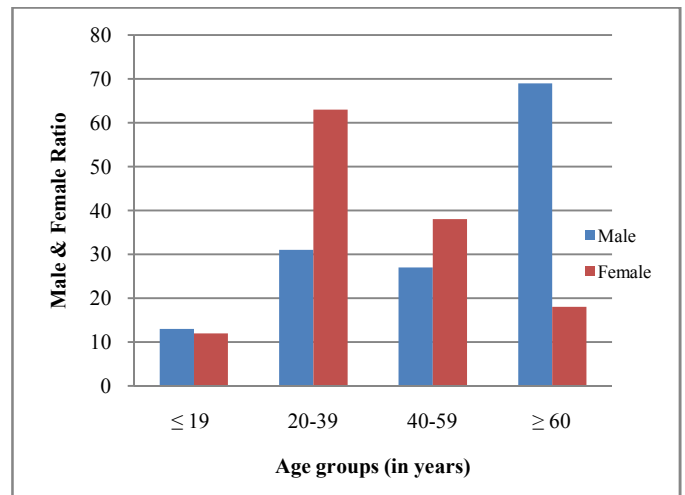


**Fig 1** Percentage distribution of uropathogens in OPD & IPD

**Table 1** Distribution of UTI patient according to Age group & Gender

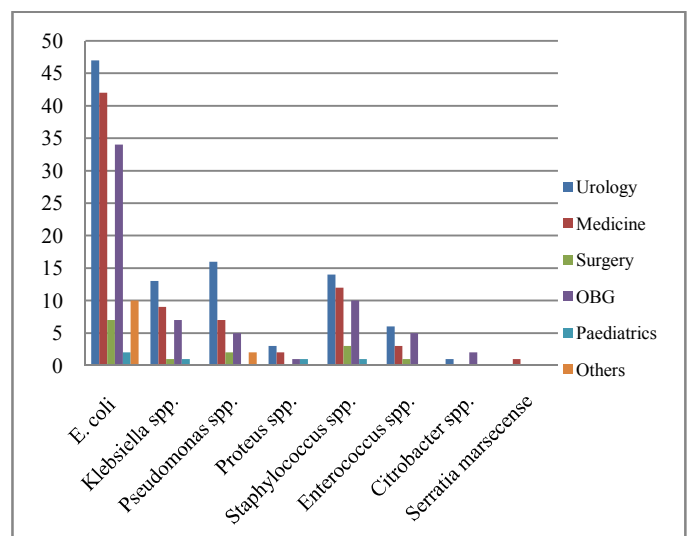
Age group(years)	Total (n=271)	% of total	Male (n=140)	Female (n=131)	Z	P
≤ 19	25	9.22	13(52.0%)	12(48.0%)	0.282	0.779
20-39	94	34.68	31(33.0%)	63(67.0%)	-4.667	<0.0001
40-59	65	23.98	27(41.5%)	38(58.5%)	-1.929	0.0536
≥ 60	87	32.10	69(79.3%)	18(20.7%)	7.732	<0.0001

Overall Chi Square=42.4; df=3; p<0.001



**Fig 2** Male & Female Ratio for UTI occurrence

In this study, the Gram negative bacilli contribute to 79.7% of the total bacterial isolates while Gram positive cocci constituted 20.3%. The predominant isolates were *E. coli* (no=142), *klebsiella spp.* (no=31), *pseudomonas aeruginosa* (no=32), *proteus vulgaris* (no=4), *proteus mirabilis* (no=3), *citrobacter spp.* (no=03) among gram negative bacteria & *staphylococcus spp.* (no=40), *Enterococcus spp.* (no =15) among gram positive bacteria. Maximum number of cases was from super speciality Urology department, followed by general medicine, obstetrics-gynaecology, general surgery, paediatrics & others.



**Fig 3** Distribution of uropathogens in different department

In present study, antibiotic sensitivity pattern revealed that maximal sensitivity were observed in Fosfomycin &

Nitrofurantoin, while other antimicrobial agents showed variable sensitivity. fosfomycin were maximally sensitive to *E. coli* (92.9%), followed by *Klebsiella pneumoniae* (90.3%), *Proteus spp.* (85.7%), *pseudomonas spp.*(81.3%) & *citrobacter spp.*(33.3%) . In gram positive isolate, Fosfomycin sensitivity was 77.5% in *Staphylococcus spp.* and 86.7% in *Enterococcus spp.* Apart from them, amikacin, ceftriaxone-sulbactam & piperacillin-tazobactam showed good sensitivity among gram negative isolates. In gram positive isolates, amikacin showed 82.5 % sensitivity against *Staphylococcus spp.*

**Table 2** Percentage distribution of antibiotic sensitivity in gram negative uropathogens

ABX	Gram Negative isolates					
	<i>E. coli</i> n=142	<i>Klebsiella</i> <i>spp.</i> n=31	<i>Citrobacter</i> <i>spp.</i> n=3	<i>Proteus</i> <i>spp.</i> n=7	<i>Pseudomonas</i> <i>spp.</i> n=32	<i>S. marcescens</i> n=1
FO	92.9	90.3	33.3	85.7	81.3	100
NIT	92.3	77.4	100	100	37.5	100
AMC	44.4	35.5	00	00	9.4	100
COT	38.7	41.9	00	00	21.9	00
CTR	34.5	22.6	00	14.3	9.4	100
CX	61.3	38.7	66.7	42.9	12.5	100
C/S	80.9	48.4	66.7	71.4	18.6	100
CFM	33.1	41.9	00	14.3	21.9	100
AK	83.8	64.5	100	57.1	56.3	100
CIP	21.8	32.3	33.3	28.6	34.4	100
MRP	69.0	70.96	33.3	42.9	43.6	100
IMP	52.1	51.6	100	42.9	40.6	100
LE	40.1	48.4	33.3	28.6	21.9	100
GEN	67.6	64.5	33.3	28.6	28.1	100
PIT	81.7	74.2	100	100	78.1	100

**Table 3** Percentage distribution of antibiotic sensitivity in gram positive uropathogens

ABX	Gram Positive isolates	
	<i>Staphylococcus</i> <i>spp.</i> (n=40)	<i>Enterococcus spp.</i> (n=15)
FO	77.5	86.7
NIT	82.5	86.7
AMC	47.5	-
COT	45	20
CTR	52.5	00
C/S	82.5	00
AK	82.5	73.3
CIP	35	00
MRP	00	00
IMP	00	00
LE	50)	20
GEN	52.5	53.3
PIT	00	00

**DISCUSSION**

The prevalence of UTI was found to be 24.6% in this study. Which is correlating with other studies from India done by M. Dash *et al* and M. Mehta *et al* showing prevalence of UTI was 34.5% and 36.68% respectively[6, 7]. However the higher prevalence was also seen in a study by Devanand *et al* (53.82%) [8]. This study showed a high prevalence of UTI in females than in males (20-39 yrs age group) (p <0.0001). In females, high prevalence of UTI is due to close proximity of the urethral meatus to the anus, shorter urethra, sexual intercourse & incontinence [9]. However, in ≥ 60 yrs age group, higher incidence of UTI was noted in males (79.3%) in compare to Female (20.7%)(p <0.0001), may be due to prostate disease & other urogenital disease. Similar observation being reported by Smita S *et al* (10) and Devanand *et al*[8]. *Escherichia coli* (52.4. %) was found to be the most common gram negative bacteria causing UTI. This result is

consistent with other studies by Devanand *et al* (42.58%) [8], Smita *et al* (61.84%) [10], Agbawa *et al* (63.3%) [11], Mulugeta *et al* (60.29%) [12], Asrat Aglu *et al* (53.69%) [13], Arghya Das *et al* (34.1%) [14].

In this study, Fosfomycin showed antibiotic sensitive to *E. coli* (92.9%), followed by *Klebsiella pneumoniae* (90.3%). In the study by Maraki *et al* [15], reported fosfomycin showed good in vitro activity against a majority of urinary isolates. The susceptibility testing for fosfomycin showed good in vitro activity against *E. coli* 98.8 % and *Klebsiella spp.* 94 %, described by Hu *et al* [16]. In India, Sahni *et al* reported 83 per cent sensitivity to fosfomycin in *E. coli* isolates [17]. According to Rajendran *et al* [18], fosfomycin was the only antibiotic that effectively inhibited 90% of the strains of *Escherichia coli* and *Klebsiella spp.* including extended spectrum beta lactamases (ESBL) producers. In a study conducted by Falgas ME *et al* [19], (96.8%) of ESBL producing *E. coli* isolates were susceptible to fosfomycin. In Pullukcu H *et al.* Study, 94.3% of clinical success was noted in the treatment of ESBL producing *E. coli* related lower UTI [20]. Immunomodulating property may aid in antimicrobial activity of Fosfomycin against ESBL producing *E. coli* [21]. Fluoroquinolones & co-trimoxazole had been found to show high resistance against isolates, which have been similarly reported in various other studies [22, 23]. Nitrofurantoin sensitivity in *E. coli* (92.3%), *Klebsiella spp.*(77.4%), *Pseudomonas spp.*(37.5%) while *citrobacter spp.*, *proteus spp.* & *Serratia marcescens* were solely 100% sensitive. whereas, among gram positive, *S. aureus* (82.5%) & *Enterococcus spp* (86.7%) sensitive. This is similar to other studies by Simon A *et al.* [24] and Lai B *et al.* [25], where 94% & 89% of the *E. coli* isolates were susceptible to nitrofurantoin respectively. Most *Proteus* species, *Serratia marcescens* and *P. aeruginosa* are intrinsically resistant [22]. Therefore, an alternate agent should be selected for them. Nitrofurantoin is also active against vancomycin sensitive enterococci (VSE) and vancomycin resistant enterococci (VRE) [26]. Nitrofurantoin has advantage over TMP-SMX and fluoroquinolone for initial empiric therapy of lower UTIs. In this study, most of the Uropathogens were susceptible to Fosfomycin & Nitofurantoin, whereas they shows high rate of resistance to conventionally used antibiotics to treat UTI.

**CONCLUSION**

Fosfomycin & Nitrofurantoin exhibits good in vitro activity against Uropathogens tested. Therefore, these two older drugs might be considered as a good treatment option for urinary tract infections. To provide optimum use, antibiotics susceptibility testing is the need of the time to preserve it for next generation.

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