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RESEARCH ARTICLE
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A STUDY ON THE ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF NITROFURANTOIN AND FOSFOMYCIN AGAINST GRAM NEGATIVE UROPATHOGENS IN A TEACHING HOSPITAL OF SOUTH BENGAL.

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ABSTRACT

INTRODUCTION- Urinary tract infections (UTIs) are the most common bacterial infection which can affect all age groups. They lead to large proportion of antibiotic consumption contributing to development of antibiotic resistance .UTIs caused by multidrug resistant (MDR) pathogens have limited treatment options. Fosfomycin (FO) and Nitrofurantoin(NIT) are broad-spectrum oral antibiotics with high urine concentration and bactericidal activity against a wide range of bacteria.Their use in complicated UTI has caused emergence of increased antibiotic resistance for these two urinary specific antibiotics.

AIM-

1. To identify the sensitivity pattern of gram negative uro-pathogens to Nitrofurantoin and Fosfomycin
2. To compare the sensitivity and resistance patterns of Nitrofurantoin and Fosfomycin in different age groups of our study population

MATERIALS AND METHODS- Isolation and identification of microorganisms from aseptically collected urine samples of UTI patients were done by standard microbiological procedures and tests.. Antibiotic susceptibility testing was done by Kirby-Bauer's disc diffusion method on Muller-Hinton agar and results interpreted according to CLSI guidelines 2024.

RESULTS- *Escherichia coli* was the most common gram negative pathogen detected (60.22%)followed by *Klebsiella pneumoniae* (25.97%).Sensitivity to Fosfomycin was high among all the gram negative pathogens but sensitivity to Nitrofurantoin was found to be lower in comparison to Fosfomycin sensitivity.

CONCLUSION- Both Nitrofurantoin and Fosfomycin are urine specific antibiotics which should be used with proper prescription and caution following the principles of antimicrobial stewardship protocol so that emergence of antibiotic resistance strains can be prevented.

KEY WORDS – Urinary tract infections, Antibiotic resistance, Fosfomycin

INTRODUCTION- Urinary tract infections (UTIs) are among the most common bacterial infections both in hospital as well as community settings[1]. They can cause significant morbidity in all age groups with an increased prevalence among women within the age of 15-24 years and above 45 years age[2]. *Escherichia coli* is responsible for majority of UTIs, followed by other important organisms like *Klebsiella pneumoniae*, *Proteus spp, Acinetobacter spp, Enterococcus spp, Pseudomonas aeruginosa* etc[3].

UTIs often lead to large proportion of antibiotic consumption which contribute to antibiotic resistance and an increasing proportion of UTIs are due to multidrug resistant (MDR) pathogens for which there are limited treatment options[4]. A lack of accurate microbiological diagnosis of infections, low availability of antibiotics and absence of antimicrobial susceptibility studies accentuate the problem of antimicrobial resistance in rural set up in developing countries due to excessive, uncontrolled use of broad-spectrum antibiotics which can negatively impact the economy and health of these societies by prolonged hospital stays and lack of treatment efficacy[1].

As antimicrobial resistance increases changes must be brought about not only in empirical therapy, but also in efforts to encourage rational use of antibiotics[5]. Fosfomycin and Nitrofurantoin are broad-spectrum cell wall inhibiting antibiotics which may be useful as oral treatment options in non-complicated UTIs due to their rapid oral absorption, high urine concentration and bactericidal activity against a wide range of bacteria[6]. Thus the present study was conducted to assess the susceptibility pattern of Fosfomycin and Nitrofurantoin against uro-pathogens.

AIM-

1. To identify the sensitivity pattern of gram negative uro-pathogens to Nitrofurantoin and Fosfomycin
2. To compare the sensitivity and resistance patterns of Nitrofurantoin and Fosfomycin in different age groups of our study population

MATERIALS AND METHODS- This is a hospital-based cross sectional study conducted in the Department of Microbiology at Tamralipto Government Medical College and Hospital, East Midnapore, West Bengal over a period of one year from July 2023 to June 2024.

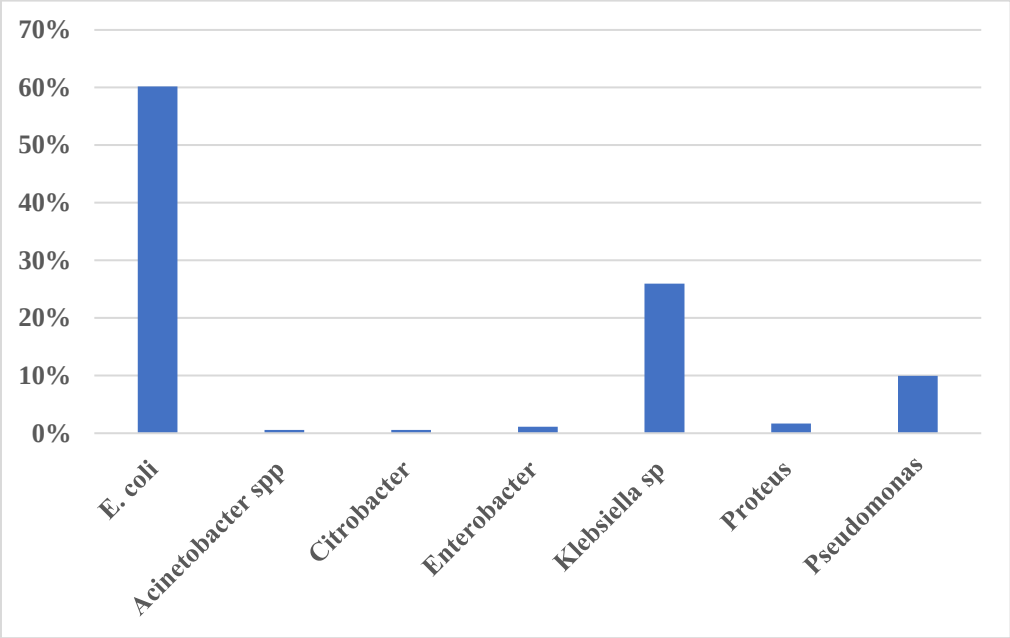
Clean catch midstream early morning urine samples collected aseptically in a sterile container from patients suffering with symptoms of UTI were received for aerobic culture in the Department of Microbiology. Isolation of microorganisms were done by standard microbiological procedures such as culturing the urine samples on cysteine lactose electrolyte deficient (CLED) agar and MacConkey agar and identification of any growth observed was confirmed by gram stain, followed by other relevant standard biochemical tests. Antibiotic susceptibility testing was done by Kirby-Bauer's disc diffusion method on Muller-Hinton agar taking 0.5 McFarland standard inoculum and antibiotic inhibition zones were interpreted according to CLSI guidelines 2024.

Results obtained from the antibiotic inhibition zones were interpreted according to CLSI 2024 guidelines and analyzed in Microsoft office excel worksheet and SPSS Ver 3.0 Software.

RESULTS- Out of the total 181 gram negative uro-pathogens which were detected from the urine samples 109 (60.22%) were Escherichia coli (E. coli), 47 (25.97%) were Klebsiella sp., 18 (9.94%)

were Pseudomonas sp., 3(1.66%) were Proteus sp., 2 (1.10%) were Enterobacter sp., 1 (0.55%) was Acinetobacter sp. and 1 (0.55%) was Citrobacter sp. (Figure 1)

Figure 1: gram negative pathogens detected in urine

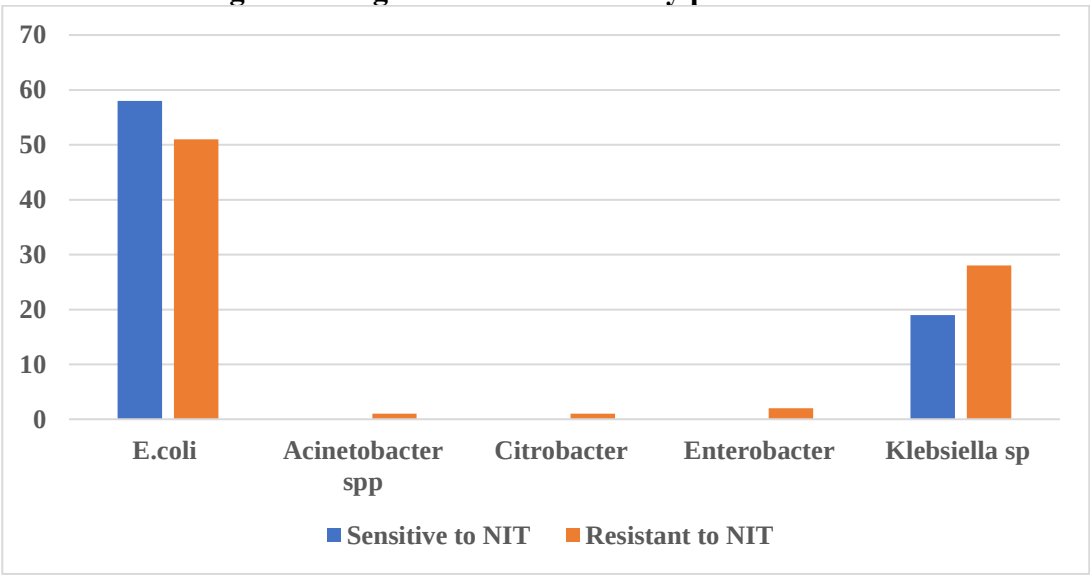


Since Proteus sp. and Pseudomonas sp. are intrinsically resistant to Nitrofurantoin (NIT) therefore they have not been tested for sensitivity to NIT. The sensitivity pattern of the gram negative uro-pathogens to NIT have been shown in Figure 2 and Table 1.

Table 1: Organism wise sensitivity pattern to NIT (n=181)

Organism	Sensitive to NIT	Resistant to NIT
E.coli (n=109)	58 (53.21%)	51 (46.79%)
Acinetobacter spp (n=1)	0 (0%)	1 (100%)
Citrobacter spp (n=1)	0 (0%)	1 (100%)
Enterobacter spp (n=2)	0 (0%)	2 (100%)
Klebsiella pneumoniae (n=47)	19 (40.43%)	28 (59.57%)

Figure 2: Organism wise sensitivity pattern to NIT



The younger age groups showed more sensitivity to NIT while the resistance to NIT increased in the higher age groups. Age group wise sensitivity pattern to NIT has been shown in Table 2.

Table 2: Age group wise sensitivity to NIT

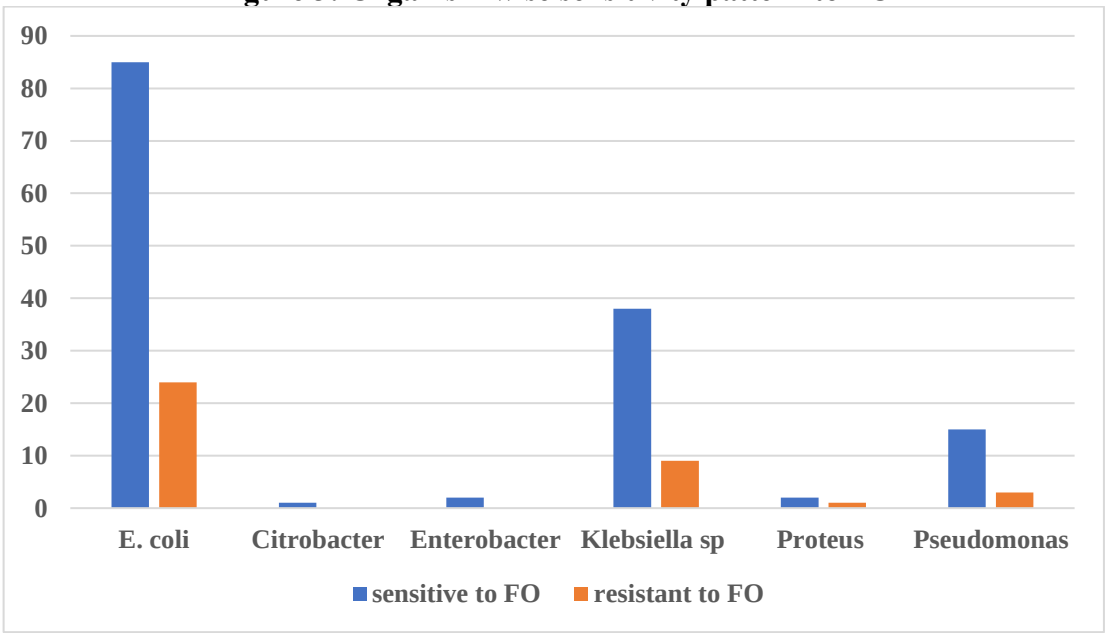
age group	sensitive to NIT	resistant to NIT
13-20 (n=24)	14 (58.33%)	10 (41.67%)
21-40 (n=83)	45 (54.27%)	38 (45.78%)
41-60 (n=46)	16 (34.78%)	30 (65.22%)
>60 (n=7)	2 (28.57%)	5 (71.43%)

Since Acinetobacter sp. is intrinsically resistant to Fosfomycin (FO) therefore they have not been tested for sensitivity to FO. The sensitivity pattern of the gram negative uro-pathogens to FO have been shown in Figure 3 and Table 3.

Table 3: Organism wise sensitivity pattern to FO (n=181)

Organism	sensitive to FO	resistant to FO
E. coli (n=109)	85 (77.98%)	24 (22.02%)
Citrobacter spp (n=1)	1 (100%)	0 (0%)
Enterobacter spp (n=2)	2 (100%)	0 (0%)
Klebsiella pneumoniae (n=47)	38 (80.85%)	9 (19.15%)
Proteus spp (n=3)	2 (66.67%)	1 (33.33)
Pseudomonas spp (n=18)	15 (83.33%)	3 (16.67%)

Figure 3: Organism wise sensitivity pattern to FO



Similar to NIT in case of FO also younger age groups showed more sensitivity to FO while the resistance to FO increased in the higher age groups. Age group wise sensitivity pattern to NIT has been shown in Table 4.

Table 4: Age group wise sensitivity to FO

age group	sensitive to FO	resistant to FO
13-20 (n=26)	24 (92.31%)	2 (7.69%)
21-40 (n=91)	75 (82.42%)	16 (17.58%)
41-60 (n=53)	38 (71.70%)	15 (28.30%)
>60 (n=10)	6 (60%)	4 (40%)

DISCUSSION- In our study the most common gram negative pathogen isolated from the urine samples was *Escherichia coli* followed by *Klebsiella pneumoniae* which is consistent to few prior studies[2,7,8]. Other gram negative pathogens isolated were *Pseudomonas spp Proteus spp, Enterobacter spp, Acinetobacter spp and Citrobacter spp.*

Proteus spp and *Pseudomonas spp*, being intrinsically resistant to Nitrofurantoin (NIT), were not tested for sensitivity to it. The other gram negative pathogens showed quite a high resistance to NIT with the two most common organisms *E.coli* and *Klebsiella pneumoniae* having 46.79% and 59.57% resistance respectively. This is in contrast to a studyby Md Shabbir Azad et. Al. where resistance to NIT was found to be quite low[9,] But few other previous studies have shown low susceptibility to NIT by *Klebsiella sp*[6,10,11]which is similar to the finding in our study. Among the one *Enterobacter spp*, one *Citrobacter spp* and one *Acinetobacter spp* all were found to be resistant to NIT.

Most of the NIT resistance was observed in older age groups >60 years and also in 40 to 60 years age group. This might be due to higher co-morbidities at this age for which more frequent hospitalization is required leading to higher exposure to antibiotics and thus development of antibiotic resistance[3].

The development of increasing resistance to NIT observed in our study is a cause of concern. Recent interest in older antibiotics like NIT has resulted in increased consumption of the drug which might cause increasing selection pressure for resistant strains and hence an overall increase in resistance towards NIT[11].

Acinetobacter spp, being resistant to Fosfomycin (FO), was not tested for sensitivity to it. The other gram negative pathogens showed a high susceptibility to FO which is a similar finding to several other studies[6,9,12].

Older patients >60 years age showed some resistance to FO, the reason for which might be due to increased frequency of hospitalization and thus exposure to antibiotics.
Thus in our study we can see that FO is effective against gram negative uro-pathogens and may be considered as a good treatment option.

CONCLUSION- Nitrofurantoin and Fosfomycin are urine specific antibiotics and their resistance patterns in our study show that they should be used with care and proper prescription following antimicrobial stewardship protocol. Over the counter misuse and overuse of these antibiotics have to be avoided.

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