

## SUSCEPTIBILITY PATTERN OF OLDER DRUGS, NITROFURANTOIN AND FOSFOMYCIN IN URINARY TRACT INFECTIONS IN GRAM NEGATIVE ISOLATES: A STUDY FROM TERTIARY CARE HOSPITAL IN SUB-HIMALAYAN REGION.

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### ABSTRACT

**Background** Urinary tract infection is the most common infection which requires medical attention worldwide. Escherichia coli being the most common etiological agent for the infection and females are more susceptible to males. The uncontrolled use of antibiotics in UTI without AST has led to an increase in drug resistance. The effect of raising resistance, treatment is again going to the older drugs which were once discontinued due to availability of newer antibiotics. This study focused on the impact of sensitivity patterns in uropathogenic bacteria for fosfomycin and nitrofurantoin respectively. This study was a retrospective study for a period of one year in the department of Microbiology, Dr. R.P. Govt. Medical College Tanda at Kangra. High susceptibility was noted for the older drugs taken in the study which concluded that Nitrofurantoin and Fosfomycin proves to be a useful treatment option for community-based treatment of patients with resistant organisms.

### INTRODUCTION

The most common community-acquired infections include Urinary tract Infections, and agents like co-trimoxazole and fluoroquinolones are commonly used in treatment of urinary tract infections. Due to the increased prevalence of drug resistance globally, there has been a surge in the efforts to identify newer treatment options or re-evaluate the existing agents for the treatment of urinary tract infections, like fosfomycin and nitrofurantoin 1-4.

Antibiotic resistance is becoming more common worldwide. This means infections are harder to treat and can lead to more deaths, illnesses and cost. Because of this, the usual antibiotics may not work and more people with these infections need to go to the hospital for stronger antibiotics. It's likely that resistance rates have gone up<sup>5-7</sup>.

There aren't many new antibiotics being developed, and most of the ones that have been approved recently can only be given through a vein. So, older antibiotics that haven't been used

much are being looked at again for treating urinary tract infections. Nitrofurantoin and fosfomycin are old drugs. One large national survey of urinary isolates from 2015 in Australia, found resistance rates in *Escherichia coli* of 43% for ampicillin, 9% for amoxicillin with clavulanic acid, 16% for cefazolin, 22% for trimethoprim, and 7% for ciprofloxacin<sup>8</sup>.

## MATERIAL AND METHODS

A retrospective study from the Department of Microbiology, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda for 1 year from June 2021 to May 2022 was done. Urine samples were plated on Cystine Lactose Electrolyte- deficient (CLED) Agar and Mc Conkey agar by standard loop method and were incubated overnight at 37 C. Urinary pathogens were identified as per standard protocol<sup>9</sup>.

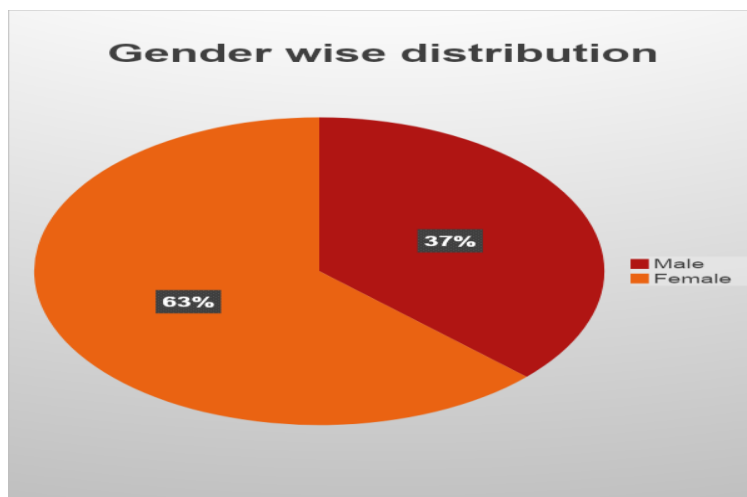
The bacterial isolates obtained were streaked as lawn culture on Mueller Hinton Agar and antibiotic susceptibility testing was performed by Kirby Bauer Disc Diffusion method as per CLSI guidelines<sup>9</sup>.

We defined a uropathogen as an organism known to be associated with signs and symptoms of UTI with  $> 10^5$  colony forming units/mL of urine. If a urine specimen grew  $> 3$  organisms, it was considered as contaminated and was excluded from the study.

The following antibiotics discs were used: Fosfomycin (200 $\mu$ g/disc), Levofloxacin (5 $\mu$ g/disc), Nitrofurantoin (300 $\mu$ g/disc), Co-trimoxazole (25 $\mu$ g/disc), and Cefazolin (30 $\mu$ g/disc). 6 Interpretative criteria from the CLSI for Fosfomycin susceptibility are only available for *Escherichia coli* (*E. coli*) and *Enterococcus faecalis*. Therefore, results for other organisms were interpreted according to the criteria for *E. coli*.

## RESULTS

A total of 6368 urine samples were collected in a duration of one year. Only 1188, 19 % samples showed significant growth (significant bacteruria/candiduria). Female to male ratio was 1.7:1. 92% of samples were from the age group of more than 18 years, 5% from age group 6 years – 18 years, 3% from the age group less than five years.(Fig. 1 & 2)



**Fig.1 Distribution on the basis of Sex.**

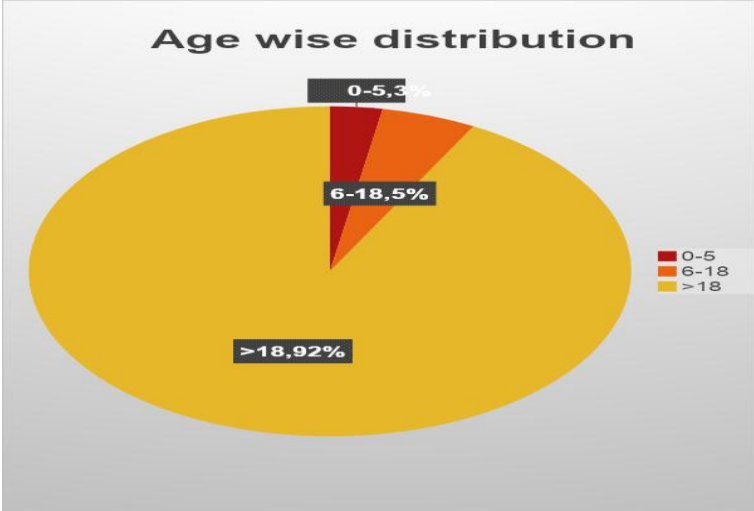


Fig.2 Distribution on the basis of Age

Gram positive bacterial isolates obtained were *Enterococcus spp.*(2.02%), *Coagulase Negative Staphylococci* (0.84%), *Methicillin Resistant Staphylococcus aureus* (1.68%) & *Methicillin Sensitive Staphylococcus aureus* (2.18%)

Gram negative bacterial isolates obtained were *Escherichia coli* (54.46%), *Klebsiella pneumoniae* (12.7%), *Pseudomonas aeruginosa* (4.96%), *Non Fermenter Group of Organisms* (2.52%), *Enterobacter spp.* (2.52%), *Citrobacter spp.* (2.10%), *Proteus vulgaris*(2.10%), *Acinetobacter baumannii* (4.88%)

Fungal isolates obtained were *Candida albicans* (2%), *Non albicans candida* (4.96%)  
(Fig. 3)

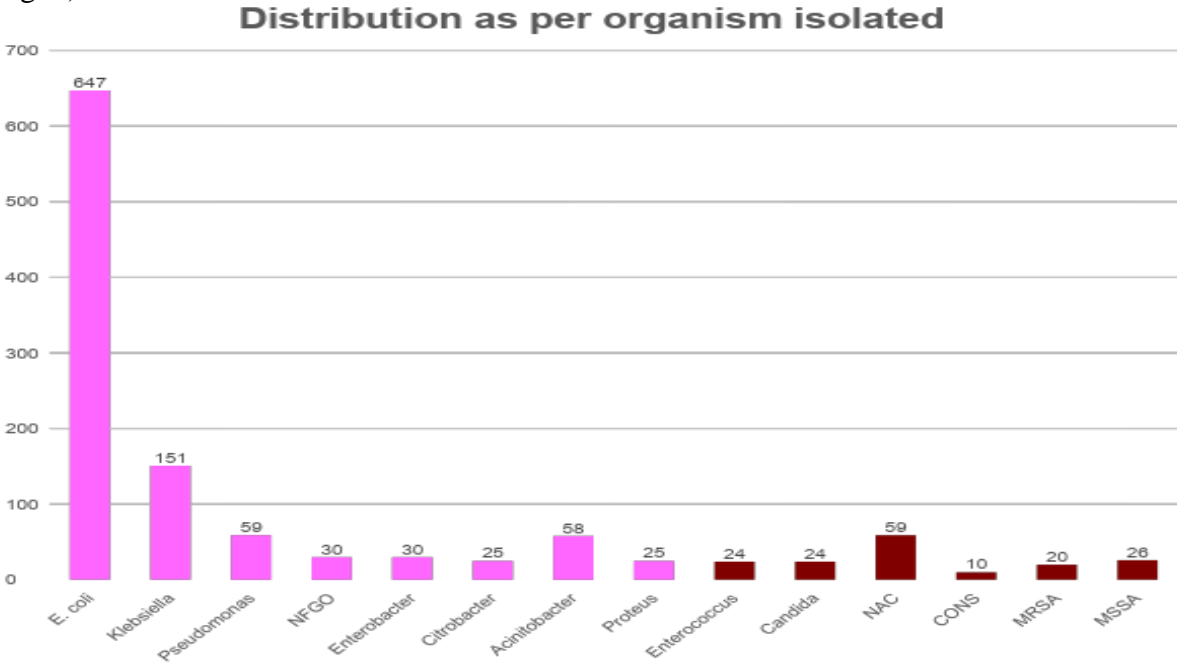


Fig. 3 Distribution as per organism isolated

Nitrofurantoin showed 97.52 % sensitivity for *Escherichia coli* and 82.78 % sensitivity for *Klebsiella pneumoniae*.

Fosfomycin showed 98.29 % sensitivity for *Escherichia coli*.( Fig. 4)

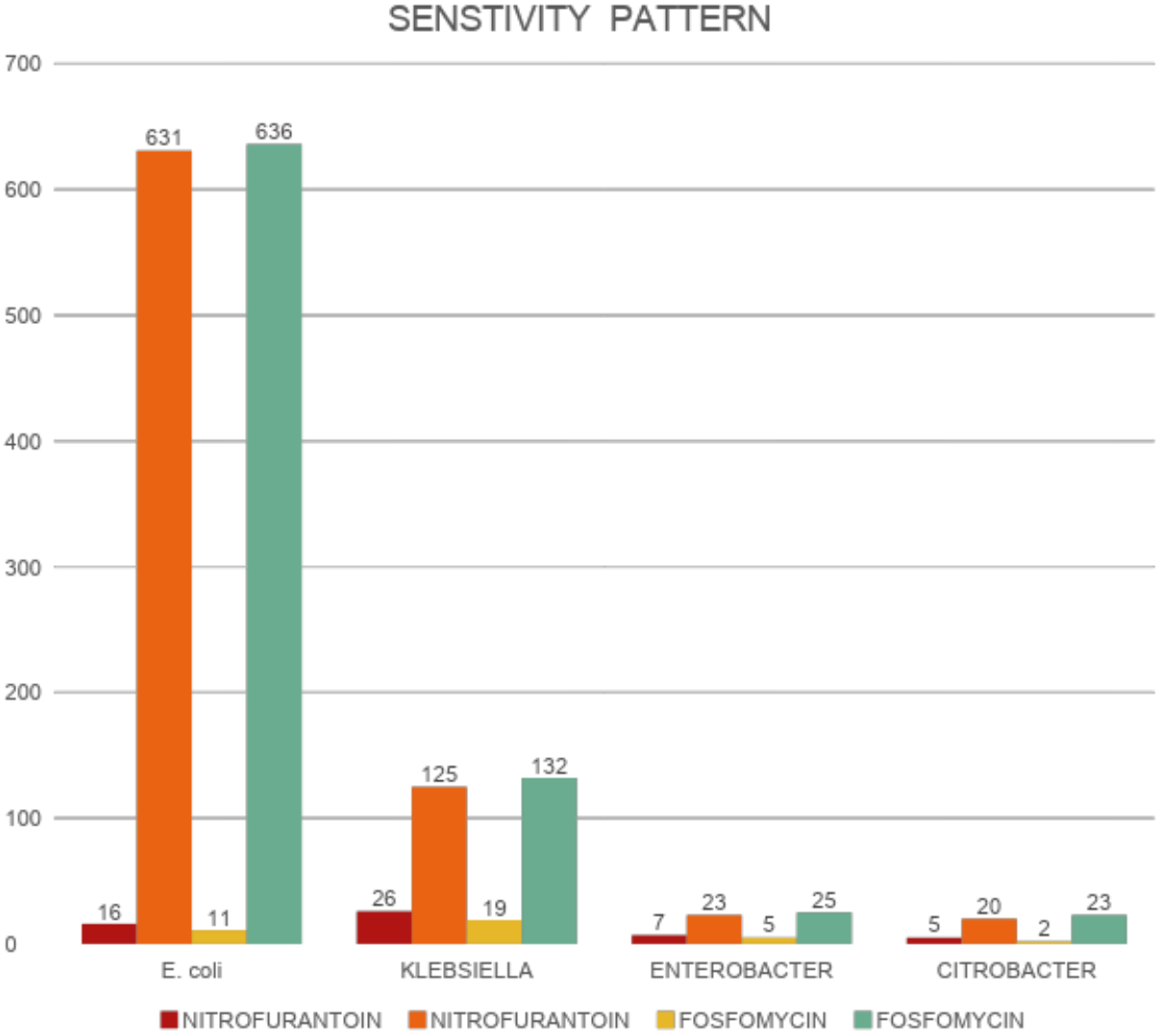


Fig. 4 Distribution as per sensitivity pattern

**Table 1: Comparison between the two drugs**

Characteristic	Nitrofurantoin	Fosfomycin
Year of discovery	1953	1969
Pharmacokinetics	High urinary concentrations Serum concentrations negligible	Long half-life with high urinary concentrations Serum concentrations inadequate for treatment of systemic infection
Mechanism of action	Not well understood, multifactorial, inhibits ribosomal protein synthesis	Inhibits pyruvyl transferase and therefore cell wall synthesis
Spectrum of activity	Mostly susceptible: E. coli, Enterococcus Variably susceptible: Klebsiella, Enterobacter, Citrobacter and Providencia Typically resistant: Proteus, Serratia, Acinetobacter, Morganella	Mostly susceptible: E. coli Variably susceptible: Klebsiella, Proteus, Citrobacter, Enterobacter, Pseudomonas and Enterococcus Typically resistant: Morganella and Acinetobacter
Resistance	Uncommon	Uncommon
Indications and dosage	Uncomplicated urinary tract infection 50–100 mg 3 times a day for 5 – 10 days	Uncomplicated urinary tract infection Single 3 g oral dose

**DISCUSSION**

Majority of the urinary tract infections are caused by Escherichia coli world wide. Our study showed similar results with the highest isolated being Escherichia coli.

The use of fosfomycin in treating urinary tract infection (UTIs) is increasing in the western world according to several studies<sup>10-13</sup>. However, in India there is limited data available on the

use of fosfomycin. In a recent study, it was found that fosfomycin showed a high sensitivity rate (99.3%) in killing the bacteria causing UTIs which is similar to what other studies have shown<sup>14 & 1</sup>

In the healthcare setups, nitrofurantoin has been prescribed for more than ten years, while fosfomycin has only been used for the past two years. Because of this difference in usage, the bacteria causing UTIs may develop resistance against nitrofurantoin

## CONCLUSION

Nitrofurantoin is suitable for uncomplicated lower urinary tract infections. Fosfomycin is a safe and effective antibacterial drug for urinary tract infections, but its use should be limited to delay the development of resistance. Nitrofurantoin and Fosfomycin proves to be a useful treatment option for community-based treatment of patients with resistant organisms.

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