Efficacy of Nitrofurantoin and Fosfomycin against Extended Spectrum Beta Lactamase Producing Uropathogens in the Era of Antibiotic Resistance: A Cross-sectional Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: Urinary Tract Infection (UTI) is one of the most common bacterial infections that require medical care. It accounts for 25% of all infections. Limited number of antibiotics are available for the treatment of UTI due to increased resistance among uropathogens. Aim of the

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study is to determine the causative agents of UTI and to evaluate the action of nitrofurantoin and fosfomycin against Enterobacteriaceae in ESBL (Extended spectrum beta-lactamase) producing strains.

Material and Methods: It is a retrospective study carried out in the department of Microbiology, MAMC, Agroha. Data related to urine culture and antibiotic susceptibility pattern from January 2023 to December 2023 was taken from the records and analysed.

Results: Out of 1648 urine samples processed, 569 showed significant bacterial growth. *Escherichia coli* (45.3%) was the most common isolate followed by *Klebsiella pneumoniae* (20.5%), *Enterococcus* (17.2%), *Staphylococcus aureus* (5%). Among the gram negative bacilli, 40% were ESBL producers. These ESBL producing strains were 99% sensitive to Fosfomycin and 75% sensitive to Nitrofurantoin.

Conclusion: The study revealed that Nitrofurantoin and Fosfomycin are very effective oral drugs for empirical treatment against gram negative uropathogens causing UTI, especially multi drug resistant strains.

1. INTRODUCTION

Urinary tract infection (UTI) is one of the most commonly encountered infection by clinicians in developing countries [1]. It accounts for 25% of all infections [2]. Every year approximately 150 million people are diagnosed with urinary tract infection worldwide [3]. Multiple factors such as old age, poor personal hygiene, pregnancy, urinary catheterization, genitourinary tract abnormalities and co-morbidities like diabetes, HIV infection contributes in prevalence of UTI [4]. It affects the both genders but it is more common in the female population. It has been assessed that more than 50% of all women experience at least one UTI during their lifetime, with 20-30% presenting with recurrent UTI due to their anatomy and reproductive physiology [5].

Clinically UTI is divided into asymptomatic, acute, chronic, complicated or uncomplicated depending upon the infectious agent, part of urinary tract involved and patient's immune response [6].

Most of the time UTI is managed empirically before the results of urine culture & antimicrobial susceptibility testing (AST) become available (as bacteriological cultures are not done aggressively). Because of many factors reports are delayed; either due to improper collection of specimens, contamination by normal flora or a delay in transit of specimen to the laboratory [7]. Empirical treatment leads to misuse of antimicrobial agent, development of multi-drug resistant organisms and failure of empirical therapy [1].

The spectrum of antimicrobial susceptibility of UTI pathogens varies from time to time and in different geographical areas, hospital to hospital, state to state and even from country to country [1]. *Escherichia coli* is the most common pathogen isolated from patients presenting with signs and symptoms of UTI, both complicated and uncomplicated UTI [8]. The indiscriminate use of antibiotics leads to emergence of multidrug resistant (MDR) pathogens which are very difficult to treat [9]. Hence, it becomes important to regularly monitor the resistance or susceptibility pattern of uropathogens, so that the guidelines for empirical therapy can be improved to include antibiotics with low resistance, aiding clinicians in proper management of UTIs with minimal therapeutic failures. The emergence of multidrug resistant (MDR) organisms has promoted re-evaluation of non-traditional antibiotics. The antimicrobial agents that are not much used in clinical practice, may be successful in treating these MDR organisms. Nitrofurantoin and Fosfomycin are the two old underrated antibiotics that attain higher concentrations in the urinary tract and have minimal side effects [10].

2. MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Microbiology, Maharaja Agrasen Medical College, Agroha, Hisar. The study was begun after receiving ethical approval from institutional ethics committee. All the urine samples received in sterile container in microbiology department from the patients with clinical features suggestive of UTI from any indoor and outdoor departments were included in the study. Samples having insignificant bacteriuria with no pus cells and samples having more than 2 isolates were excluded from the study.

The data from January 2023 to December 2023 was collected from the medical records. It contains information about the patient's age, sex, reports of urine culture, and their antibiotic susceptibility profiles. The statistical analysis was done taking 5% level of significance ($\alpha = 5\%$) and power ($1-\beta$) of the statistical test at 80%. Then, the data was entered and compiled in MS Excel sheet and further exported to Statistical Package for Social Sciences (SPSS) version 20.0 for appropriate analysis.

All the samples were processed within 30 minutes of receipt. Direct microscopy of the un-centrifuged urine sample was done for the presence of pus cells, RBCs, bacteria, budding yeast cells, crystals & casts. Using a semi-quantitative approach and a standard loop (0.01 ml), urine samples were inoculated on CLED agar (cysteine lactose electrolyte-deficient media, Hi-Media India) and incubated aerobically at 37°C for 18 to 24 hours. The plates showing significant growth as per the Kass count (single species count of >10^5 CFU/ml of urine) were processed further for identification and AST pattern on VITEK - 2 compact by Biomeriux.

The isolates were further examined for the ability to produce extended spectrum beta lactamases (ESBL), in accordance with the CLSI recommendations. Ceftazidime (30µg) and Ceftazidime /clavulanic acid (30 µg /10µg) discs were used as confirmatory test for screening of ESBL. The results were interpreted as per CLSI guidelines.

3. RESULTS

Out of 1648 urine samples processed for culture and sensitivity over a period of one year from January 2023 to December 2023, 569 (34.5%) samples showed significant bacterial growth. Among the 569 samples, 234 (41.3%) were of male and 335 (58.8%) were of female patients (Fig. 2). Significant bacterial growth was found to be greater in patients in the age group of 21-30 years (Fig. 1).

Of the samples showing growth, gram negative isolates were 418 (73.5%) and gram positive isolates were 151 (26.5%). *Escherichia coli* (45.3%) was the most common isolate followed by *Klebsiella pneumoniae* (20.5%), *Enterococcus* (17.2%), *Staphlyococcus aureus* (5.9%) (Table 1). Among the gram negative bacilli, 167 (40%) were ESBL producers (Fig. 3). These ESBL producing strains were 99% sensitive to fosfomycin and 75% sensitive to nitrofurantoin (Table 2).
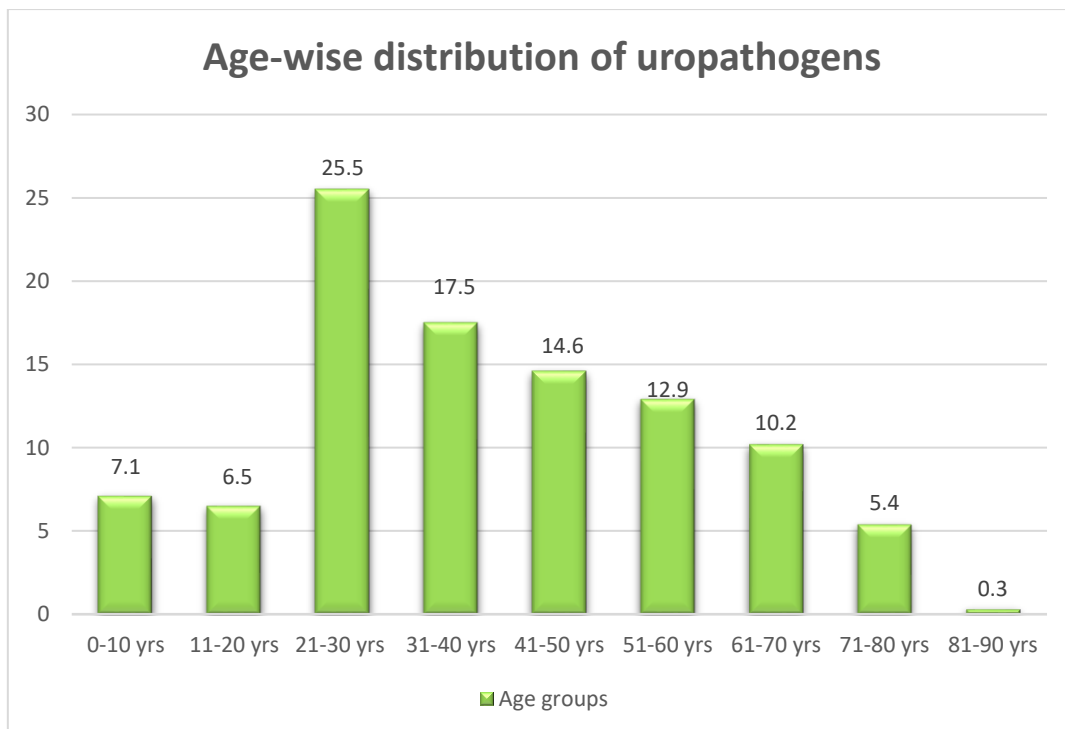

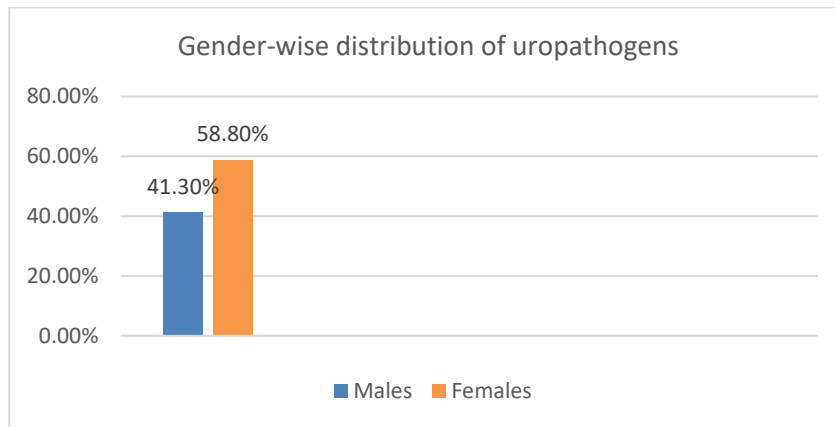**Fig. 1. Age-wise distribution of uropathogens**
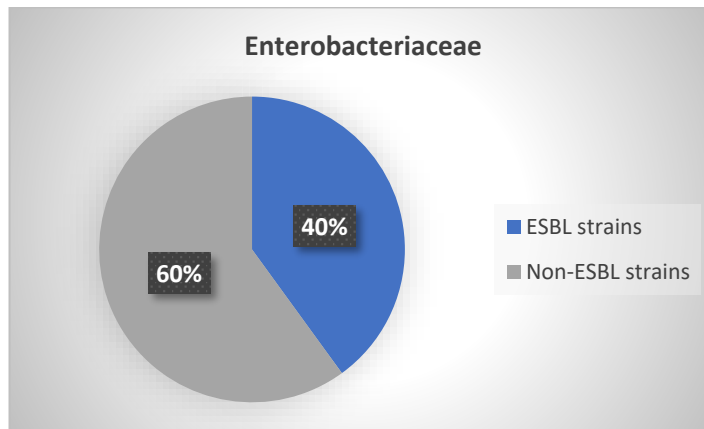
Fig. 2. Gender-wise distribution of uropathogens

Fig. 3. Distribution of ESBL and Non-ESBL strains among Enterobacteriaceae

Table 1. Distribution of various bacterial isolates from urine

Bacterial isolates	No of strains	Percentage
Escherichia coli	258	45.3
Klebisella pnemoniae	117	20.5
Enterococcus species	98	17.2
Staphylococcus aureus	29	5.09
Coagulase negative staphylococci	24	4.2
Pseudomonas	23	4.04
Proteus	11	1.9
Acinetobactor sp	9	1.5
Total	569	100

Table 2. Susceptibility pattern of Nitrofurantoin and Fosfomycin among ESBL and Non-ESBL strains

	Nitrofurantoin		Fosfomycin	
	Sensitive	**Resistant**	**Sensitive**	**Resistant**
ESBL strains	75%	15%	91%	9%
Non - ESBL strains	85%	25%	99%	1%

4. DISCUSSION

Urinary Tract Infections (UTI) are one of the most common bacterial infections that require medical care. UTI is defined as a disease caused by microbial invasion of the urinary tract that extends from renal cortex of the kidney to the urethral meatus. It is broadly classified into two types – lower UTI and upper UTI [11]. Depending upon the source of infection, it can be – healthcare associated and community acquired. In hospitals, UTI is most common HAI's (hospital acquired infections), accounting for 35% of the total HAI's [11].

In our study, the prevalence of UTI was estimated to be 34.5%. The results are comparable to those found in Rawalpindi by Khan MI [12]. *Escherichia coli* (45.3%) was the most frequent pathogen found in patients displaying signs and symptoms of UTI, followed by *Klebsiella pneumoniae* (20.5%). The findings were in conformity with earlier research conducted by Pardeshi et al, Karishetti et al, Vijayganapathy et al and Banerjee et al, where 53.77%, 56.6%, 66.6%, 60.67 isolates were *E. coli* and 27.4%, 13%, 15.7%, 18.82% were *K. pneumoniae* respectively [13-16]. In the present study, *Enterococcus* (17.2%) was found to be the most prevalent gram-positive bacterium responsible for UTIs, followed by *Staphylococcus aureus* (5.09%). These results are in accordance with previous studies [14,16,17]. However, some studies have found *Staphylococcus aureus* to be the most common gram-positive agent responsible for UTI [12].

Because of indiscriminate use of antibiotics, there is increasing emergence of antibiotic resistance among urinary pathogens. Thus, making it a major public health issue. Therefore, there is a need to periodically monitor the causative agents of UTI and their susceptibility pattern for effective empirical treatment of patients suffering from UTI [13]. Nitrofurantoin and Fosfomycin are the two long-gone, under-appreciated antibiotics that have less side effects and can attain greater concentrations in the urinary system. Fosfomycin is primarily used to treat UTI's. especially those caused by *Escherichia coli* and *Enterococcus faecalis* [18]. Fosfomycin acts by inhibiting the enzyme phosphoenolpyruvate synthase, disrupting the synthesis of bacterial cell wall.

In this study, we have found that the sensitivity of nitrofurantoin against the ESBL strains was 75%, which is comparable to studies conducted by Kothari et al (75.6%), Sardar et al (82.3%) and Patel H et al (72.33%) [3,10,19]. Whereas, the sensitivity of fosfomycin in our study is 91% for the ESBL strains. These results are in harmony with other studies conducted by Kanaujia et al, Pai et al, Sharma S et al, Jain R et al, Tulara NK et al, Patel B et al, where the sensitivity to fosfomycin is reported as 65.65%, 93.38%, 99.3%, 94.48%, 99.6% and 79.16% respectively [1,8,20-23].

5. CONCLUSION

In the current study, nitrofurantoin and fosfomycin demonstrate good in-vitro efficacy against the most frequently isolated uropathogens. Fosfomycin has exhibited more sensitivity towards ESBL strains as compared to nitrofurantoin. Also, fosfomycin is more convenient for the patients due to its availability as an oral, single-dose formulation. Both medications can be used for empirical treatment of UTI, especially those caused by ESBL strains. In order to prevent the development of antibiotic resistance, clinicians should prescribe these drugs judiciously.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was begun after receiving ethical approval from institutional ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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