

Frequency of uropathogens showing resistance to Nitrofurantoin

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Abstract

Urinary tract infection (UTI) caused by bacteria is the commonest infection accountable for the unforeseen healthcare cost throughout the globe. Nitrofurantoin is being studied as a solution to the perpetually increasing threat of antimicrobial resistance. The objectives of this study were to determine the frequency of urinary isolates causing UTI and their susceptibility pattern against Nitrofurantoin. Data of all isolates reported as uropathogens from April 1, to December 31, 2021, was collected through Electronic Medical Record system of Shalamar Hospital, Lahore. Results of Nitrofurantoin susceptibility were recorded to find the resistance pattern of bacterial isolates. Out of a total of 3,221 samples, 672 (20.9%) were positive with significant bacteriuria. Of the positive samples, 418 (62.2%) were collected from females and 254 (37.8%) from males, with female to male ratio of 1.65:1. The number of female patients was higher in adult age. Of the positive samples, *E. coli* was the commonest isolate seen in 390 (58%) of samples, followed by *Enterococcus spp.* 92 (13.7%), *Klebsiella spp.* 86 (12.8%), *Pseudomonas spp.* 35 (5.2%), *Staphylococcus saprophyticus* 24 (3.6%), *Proteus spp.* 21 (3.1%), *Citrobacter spp.* 15 (2.2%), and *Acinetobacter spp.* 9 (1.3%). Overall, 587 (87.4%) isolates were sensitive to Nitrofurantoin. However, it showed increased resistance to 28 (32.6%) isolates of *Klebsiella spp.* *E. coli* remains the commonest uropathogen. In conclusion, Nitrofurantoin can be used to treat UTI caused by common bacterial pathogens except *Klebsiella spp.*

Keywords: Antimicrobial, Bacteriuria, Nitrofurantoin, Uropathogens, UTI.

DOI: <https://doi.org/10.47391/JPMA.7616>

Submission completion date: 10-08-2022

Acceptance date: 20-02-2023

Introduction

Urinary tract infections (UTIs) are among the most frequent bacterial infections affecting human beings all over the world. Every year hundreds of millions of people are affected with UTI worldwide and a vast majority of such

infections are caused by bacterial pathogens. Unfortunately, inappropriate use of antibiotics has been causing an ever-increasing resistance of bacteria against commonly used antibiotics. Nitrofurantoin, although an old drug, has gained importance as a potential solution to be used against susceptible uropathogens because even after widespread universal use for more than six decades, it has retained good activity against common uropathogens of uncomplicated UTIs.¹

Uropathogens have specialised properties, such as the synthesis of adhesins, siderophores and toxins, that allow them to colonise and invade the urinary tract. Recurrent UTIs are a prominent cause of morbidity in the female population. Frequent relapses of UTIs can lead to pyelonephritis with sepsis, pre-term child birth, and concerns regarding inappropriate antimicrobial treatment practice, resulting in enhanced antibiotic resistance. UTIs are mostly caused by bacteria belonging to the *Enterobacteriaceae* family, mostly *Escherichia coli* and *Klebsiella species*. Certain other bacteria including *Pseudomonas aeruginosa*, *Staphylococcus saprophyticus* and *Enterococci* are also involved. However, about 80% of uncomplicated UTIs are caused by uropathogenic *E. coli* (UPEC) all over the globe.² Since uropathogens are developing resistance to the currently available antibiotics, it is time to consider alternative options for the treatment of UTIs.

Nitrofurantoin is considered an approved antibiotic for treating uncomplicated UTIs. It is effective against common gram-positive as well as gram-negative bacteria. It is a synthetic antimicrobial agent produced from furan and an added nitro group and a side change having hydantoin. It has been used for the treatment of lower urinary tract infections until the 1970s when Trimethoprim-Sulfamethoxazole and newer beta-lactam antibiotics became available. It has several properties including fewer interactions with other drugs, low threat for allergic reactions, and low risk of developing resistance. However, Nitrofurantoin resistance, if present, could indicate extensive drug-resistance in *Enterobacteriaceae*.³

Since bacterial resistance is uncommon against Nitrofurantoin and because of fewer side effects, it is considered more suitable as compared to other drugs including Fosfomycin for treating lower UTIs. Moreover, the

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efficacy of Nitrofurantoin does not differ between ESBL-producing and non-ESBL-producing *E. coli* strains.⁴ Keeping in view the potential use of Nitrofurantoin in the treatment and prophylaxis of UTIs, we aim to determine the frequency of common uropathogens and their susceptibility to Nitrofurantoin.

Patients and Methods

The study design was descriptive retrospective. The data of all bacterial isolates reported as uropathogens was collected through Electronic Medical Record system of Shalamar Hospital, Lahore. Non-probability consecutive technique was used to collect time-based samples from April 1, to December 31, 2021. The data of urine samples from patients of both genders and all ages submitted for cultures during the study period was collected from April 1 to 30, 2022. The captured data was organised for analysis, writing the results and discussion from May 1, to June 30, 2022. Samples showing pure and significant growth of bacterial uropathogens were included. Cultures showing mixed growth or growth of *Candida* species and duplicate samples from the same patient during the same period of illness were excluded. All samples were processed using standard microbiological procedures for culture of bacteria. The antimicrobial susceptibility testing was done using Kirby-Bauer disc diffusion method with a panel of antibiotic discs including Nitrofurantoin. Antibiotic susceptibility was represented as sensitive and resistant by using the diameter of zone of inhibition according to the Clinical Laboratory Standard Institute (CLSI) guidelines of 2020. The data analysis involved transcription, preliminary data inspection, content analysis, and interpretation. Statistical analysis was done by descriptive statistics using ratio and percentages. Microsoft Excel was used to generate tables. Qualitative variables were expressed as rates and percentages. Institutional Review Board (IRB) approved the study vide letter No. SMDC-IRB/AL/01/2022 dated 10.01.2022.

Results

A total of 3,221 urine samples were submitted to the Microbiology Laboratory of Shalamar Hospital for culture and sensitivity testing during the study period. Of all, 672 (20.9%) samples were positive with significant bacterial growth. Out of the positive samples, 418 (62.2%) were collected from female and 254 (37.8%) were collected from male patients, with female to male ratio of 1.65:1. Overall, the number of female patients was high only in the age group where females are in their reproductive period and sexually more active.

Out of all positive samples, *E. coli* was the most common isolate which was present in 390 (58%) of the samples,

Table-1: Type and frequency of uropathogens isolated (n=672).

Type	n (%)
1) <i>E. coli</i>	390 (58.0)
2) <i>Enterococcus spp.</i>	92 (13.7)
3) <i>Klebsiella spp.</i>	86 (12.8)
4) <i>Pseudomonas spp.</i>	35 (5.2)
5) <i>Staphylococcus saprophyticus</i>	24 (3.6)
6) <i>Proteus spp.</i>	21 (3.1)
7) <i>Citrobacter spp.</i>	15 (2.2)
8) <i>Acinetobacter spp.</i>	9 (1.3)
Total	672 (100)

Table-2: Nitrofurantoin susceptibility of urinary isolates (n=672).

Uropathogen	Resistant n (%)	Sensitive n (%)
1) <i>E. coli</i> (n=390)	24 (6.2)	366 (93.8)
2) <i>Enterococcus spp.</i> (n=92)	13 (14.1)	79 (85.9)
3) <i>Klebsiella spp.</i> (n=86)	28 (32.6)	58 (67.4)
4) <i>Pseudomonas spp.</i> (n=35)	7 (20)	28 (80)
5) <i>S. saprophyticus</i> (n=24)	3 (12.5)	21 (87.5)
6) <i>Proteus spp.</i> (n=21)	4 (19)	17 (81)
7) <i>Citrobacter spp.</i> (n=15)	3 (20)	12 (80)
8) <i>Acinetobacter spp.</i> (n=9)	3 (33.3)	6 (66.7)
Total	85 (12.6)	587 (87.4)

followed by *Enterococcus spp.* in 92 (13.7%), *Klebsiella spp.* in 86 (12.8%), *Pseudomonas spp.* in 35 (5.2%), *Staphylococcus saprophyticus* in 24 (3.6%), *Proteus spp.* in 21 (3.1%), *Citrobacter spp.* in 15 (2.2%) and *Acinetobacter spp.* in 9 (1.3%) of samples (Table-1). Regarding the antimicrobial susceptibility rate of each uropathogen against Nitrofurantoin, 587 (87.4%) isolates showed sensitivity to Nitrofurantoin, whereas 85 (12.6%) were resistant. However, it showed higher resistance to *Klebsiella spp.* in 28 (32.6%) of isolates (Table-2).

Discussion

The present study revealed that the frequency of UTI is more common in females as compared to males. These findings are reinforced by similar studies conducted at different places wherein they have also reported a higher infection rate in females as compared to males.⁵ Females of younger and adult age groups are more prone to UTIs as compared to older age group. This may possibly be due to the fact that they are usually married and are sexually active. Several studies have documented that UTIs are caused most frequently by uropathogenic *Escherichia coli* (UPEC). Other important uropathogens include *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus saprophyticus*, *Enterococcus spp.*, *Proteus spp.* and *Enterobacter spp.*⁶ The present study has also shown that *E. coli* was the most common isolate which was present in 58% of the samples, followed by *Enterococcus* in 13.7%, *Klebsiella* in 12.8%, *Pseudomonas* in 5.2%, *S. saprophyticus* in 3.6%, *Proteus* in 3.1%, and *Citrobacter* species in 2.2% of

the samples. Such results are held by many studies conducted previously.²

Since long Nitrofurantoin has been commonly used as an effective drug in the treatment of urinary tract infections (UTIs). Many scholars have provided guidelines to use Nitrofurantoin as the first-line treatment for lower UTIs.⁷ The present study revealed that overall 87.4% isolates were susceptible to Nitrofurantoin. Distinctly however, it showed high resistance to *Klebsiella* spp (32.6%) and *Acinetobacter* species (33.3%). Since *Acinetobacter species* is not a common uropathogen, hence, based upon a comparison of the results obtained in our study it can be concluded that Nitrofurantoin may be a good option to treat UTIs caused by common uropathogens with the exception of *Klebsiella* species in our healthcare facility. A study on antimicrobial susceptibility patterns of uropathogens isolates done in India showed that among 1,372 urinary isolates, 86.7% of *E. coli*, 89.9% of *S. aureus*, 92.3% of *Enterobacter*, 88.6% of *Klebsiella*, and 90% of *Enterococcus* species were susceptible to Nitrofurantoin.⁸ Another such study conducted in Bangladesh also showed the high susceptibility to Nitrofurantoin (83.9%) which can be adapted for empirical treatment of UTIs.⁹ A similar study conducted in Rawalpindi had shown that out of 144 *Enterococci*, 127 (88%) were sensitive to Nitrofurantoin.¹⁰ However, there is a need to remain vigilant in the use of this drug because a recent study conducted in India had shown highest resistance in *Klebsiella species* (44.61%) isolated from urine.¹¹ Nevertheless, Nitrofurantoin is an antibiotic medication that can be used for the treatment of lower UTIs as it is effective against most gram-positive and gram-negative bacteria.

Limitations of the study: Since this study was focussed on sensitivity of uropathogens against Nitrofurantoin, comprehensive data regarding other antimicrobials was not covered.

Conclusion

E. coli remains the most common uropathogen followed by *Enterococcus* and *Klebsiella* spp. The majority of uropathogens were recovered from females in their adult age group. Nitrofurantoin can be used to treat UTIs caused by these pathogens except *Klebsiella* spp.

Recommendation: It is recommended that culture and susceptibility testing must be done to avoid misuse or overuse, and ensure appropriate use of this drug and other antimicrobials.

Disclaimer: The article has not been presented in any conference or published in any journal.

Conflict of interest: None.

Funding disclosure: The author received no financial support for the research, authorship, and/or publication of this article.

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