

ORIGINAL ARTICLE

Urinary Tract Infection and Antibiotic Sensitivity to Culture Most Commonly to Nitrofurantoin and FosfomycinTAUSIF AHMAD¹, LIAQUAT ALI KHAN², NOORSHAD KHAN³, FARMAN KHAN⁴, IFRANULLAH KHAN⁵, SAEED UDDIN⁶¹Consultant Urologist PAEC General Hospital Islamabad²Consultant General Surgeon Timergara Teaching Hospital Timergara^{3,4,5}Consultant Urologist Timergara Teaching Hospital Timergara⁶M.Phil Biochemistry Khyber Medical UniversityCorresponding author: Tausif Ahmad, Email: Tausifkmc@gmail.com, Cell: 03339391968**ABSTRACT****Objective:** To document susceptibility to Fosfomycin and nitrofurantoin among uropathogens isolated from the OPD and Emergency Room of PAEC General Hospital Islamabad.**Material and Methods:** The duration of this study was from March 2019 to July 2019, bacteria isolated from urine samples of OPD and emergency room patients suffering from pyuria were evaluated for susceptibility to antibiotic drugs such as nitrofurantoin and Fosfomycin. The medical records of the patients were obtained from hospital record and reviewed for uropathogens and other antimicrobial susceptibilities. The UTIs patients were categorized as complicated and uncomplicated UTIs.**Results:** This research study enrolled a total of 297 UTI patients with positive urine cultures. Complicated UTIs and uncomplicated UTIs were found in 228 and 69 patients respectively. The *Escherichia coli* (*E. coli*) (70.1%) and *Klebsiella pneumoniae* (15.5%) was the most common pathogens. The susceptibility of *E. coli* and *K. pneumoniae* to Fosfomycin and nitrofurantoin was high.**Conclusion:** The uropathogens in PACE general Hospital Islamabad have higher susceptibilities to antibiotics Fosfomycin than to nitrofurantoin.**Keywords:** Susceptibility, Urinary Tract Infection, Fosfomycin, Nitrofurantoin, Uropathogens.**INTRODUCTION**

Urinary tract infection (UTI) is the most prevalent infectious diseases after respiratory and gastrointestinal infections, If UTIs are failed to diagnose and treated properly at initial stages, and it leads to chronic infection that causes kidney damage in the long term ⁽¹⁾. It is caused by the microorganisms in the urinary tract. Urinary tracts consist of kidneys, ureters, bladder and urethra that collect urine and excrete it from the body through urethra after storing in the bladder ⁽²⁾. Globally, about millions of people are affecting annually by the UTI and also considered one of the primary causes of Gram-negative bacteremia. *E.coli* and *K. pneumoniae* are the predominant pathogens that are commonly responsible to cause UTI in human ⁽³⁾. Antimicrobial resistance is increasing day by day and causing infections specially UTI that is associated with increase mortality rate, disease and is very costly.

The antibiotic Nitrofurantoin and Fosfomycin are used initially in the UTI treatment ⁽⁴⁾. Because of high resistance of pathogens to other antibiotics commonly used, the anti-biotics such as Fosfomycin trometamol and nitrofurantoin were tried as substitute drug to treat infection. Nitrofurantoin and Fosfomycin was introduced since 1953 and 1969 respectively ⁽⁵⁾. Fosfomycin is still used as a first-line treatment drug for uncomplicated UTI ⁽⁶⁾. Both Nitrofurantoin and Fosfomycin are considered safe and effective for the treatment of UTI. Studies shows that *E. coli* was the most common pathogen in many countries that is responsible to cause UTIs ^(7, 8). UTI was defined as sign and symptoms of infection and the presence of >105 colony-forming units (CFU) per ml of an uropathogen in a patient urine sample ⁽⁴⁾.

Significance and Research Gap: There is the need of the modern world to replace old and ineffective antibiotic and introduced new and affective antibiotic for the treatment of infections.

Objective: The main objective of this research study was to evaluate and determine the sensitivity of the most important uropathogen (*Escherichia coli*, *Klebsiella pneumoniae*) to antibiotics Fosfomycin and Nitrofurantoin.

MATERIAL AND METHOD

A total 297 individuals suffering from UTI came to PAEC (Pakistan atomic energy commission) general hospital Islamabad from March 2019 to July 2019. All the enrolled patients were diagnosed and treated here. Their clinical data were mark out from hospital

medical record department and studied thoroughly. Urine samples were collected from different departments such as Primary Care Unit, Surgery Clinic, Outpatient Department, Obstetrics and Gynecology Clinic (OB-GYN), General Practice Clinic, and Emergency Room. The pathogenic bacteria isolated from urine specimens of UTI affected patients were evaluated for susceptibility to antibacterial drugs like nitrofurantoin and Fosfomycin. A urine sample is collected from the UTI affected patients by means of catheterization by means of the midstream clean-catch technique and sent for culture to microbiology laboratory of PEAC general hospital Islamabad in order to identify the bacteria. Urine analysis and urine culture were performed. The study protocol was approved by the Ethics Committees of the PEAC general hospital. And written informed consent was obtained.

Data Collection: All the demographic and clinical data were collected according to predesigned questionnaire which was based on the number of urine culture specimens collected from the patients coming to our setup.

Microbiology: The collected urine from all UTI patients were placed on a standard loop (10-microliter loop) and inoculated on Mac Conkey medium and blood agar. Then incubated over night at 37 °C in ambient air. The bacterial growth is considered to be ≥105 CFU/mL. Standard biochemical laboratory procedures were used to identify bacteria.

Susceptibility Testing: The antibiotic susceptibility test known as the Kirby Bauer method was used to determine the choice of antibiotic. For yeast the susceptibility test was not performed in order to eradicate duplication. The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) version M100-S21. The antibiotic discs used were for the following antibiotics ceftriaxone, amikacin, cefotaxime, ceftazidime, cefuroxime, tazocin, cotrimoxazole, imipenem, ampicillin, cefoxitin, cephalothin, gentamicin, norfloxacin, meropenem, Fosfomycin and nitrofurantoin. All the antimicrobials were placed after drying the plate for 3 to 5 minutes and incubated at 37 °C for 24 hours. The CLSI interpretation breakpoint for Fosfomycin sensitivity and Nitrofurantoin sensitivity is at least 16 and 17 mm, intermediate is between 13-15 and 15-16 mm and resistant is at most 14 mm respectively. Disc diffusion is required for Fosfomycin Antimicrobial Susceptibility Testing and was performed according to the CLSI recommendations. Reference strains of *E. coli*, ATCC 25922, was used as control for the antimicrobial susceptibility tests.

RESULTS

In our research work total 297 patients with UTIs and a positive uro culture were enrolled. The demographics and patients' characteristics are shown in Table 1. There were 122 (41.1 %) male and 175 (58.9%) female with a mean age of 34.8 s shown in table 1 and figure 1. The UTIs patients were divided into complicated and uncomplicated UTIs. In our enrolled patients 228 (76.8) were suffering from complicated UTIs and 69 (23.2) were suffering from uncomplicated UTIs. And urine collection method for majority of patients were mid-stream method. Table 2 shows that E. coli (70.1%) was identified in most of the samples and followed by another common microorganisms K. pneumoniae (15.5%). The remaining microorganism was identified is trace amount.

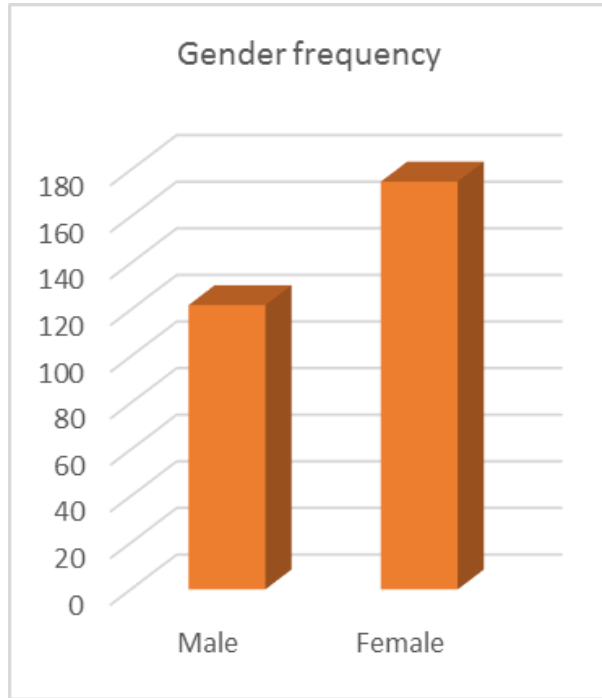


Fig 1: Bar graph showing gender frequency.

Table 1: Patient Demographics at Enrollment.

Variables	N	%
sex		
Male	122	41.1
Female	175	58.9
Mean age	34.8	-
OPD Attendant		
Urology OPD	144	48.4
OB-GYN	105	35.4
Emergency room	48	16.2
Antibiotic Treatment		
Fosfomycin	140	47.1
Nitrofurantoin	47	15.8
Other	110	37
Classification of UTIs		
Complicated UTIs	228	76.8
Uncomplicated UTIs	69	23.2
Urine collection method		
Midstream urine	241	81.1
Catheter	56	18.9

Table 4 shows the relationship between the samples collected from the OPD with the highest number of UTIs cases and the susceptibility results to Fosfomycin and nitrofurantoin. Overall, the susceptibility to Fosfomycin was greater than 93.5% in all OPD cases. For nitrofurantoin the susceptibility in all OPD cases was about 42.3-76.3%,

Table 2: Susceptibility of Samples Collected at The Outpatient Departments (OPD) To A Certain Dose of Antibiotic Fosfomycin And Nitrofurantoin.

OPD	Frequency	Fosfomycin (%)	Nitrofurantoin (%)
Urology OPD	144	100.0	67.7
OB-GYN	105	97.1	42.3
Emergency Room	48	93.5	76.3
Total	297	97.2	74.1

Table 3: Susceptibility of Complicated and Uncomplicated Urinary Tract Infections (UTIs) To Fosfomycin and Nitrofurantoin.

Classification of UTIs	N	Fosfomycin (%)	Nitrofurantoin (%)
Complicated	228	97.0	71.2
Uncomplicated	69	97.7	81.8

Table 4: Prevalence of Uro-Culture Pathogens

Bacteria	% (n=297)	95% CI
Escherichia coli	70.1	66.7-76.7
Klebsiella pneumoniae	15.5	12.8-21.2
Enterobacter cloacae	2.2	0.9-4.4
Enterococci	2.2	0.9-4.4
Citrobacter koseri	1.8	0.7-4.0
Proteus mirabilis	1.2	0.3-3.1
Klebsiella oxytoca	0.9	0.2-2.7
Serratia marcescens	0.9	0.2-2.7
Citrobacteria amalonaticus	0.6	0.7-2.2
Others	1.5	0.5-3.6

CI=confidence interval,

Others: E. Aerogenes, Pantoea agglomerants, Salmonella

DISCUSSION

Globally, UTI is one of the most common infectious diseases. Antimicrobial resistance is increasing with the passage of time. Antimicrobial resistance (AR) is a natural phenomenon that represents a major threat to Public Health, leading to an increase in healthcare costs, to therapeutic failure and sometimes to death⁽¹⁰⁾. The patterns of antimicrobial resistance also vary over time and in different regions of the world, the antibiotic treatment of infections should be according to the native sensitivity and resistance patterns. In 1991, the IDSA recommended a clinical practice guideline to treat women with acute uncomplicated cystitis⁽¹¹⁾. Due to resistant to old first line drugs the researcher is trying to look for more effective drugs. Therefore, it is the need of the modern world to replace old and ineffective antibiotic and introduced new and affective antibiotic for the treatment of infections. AR was considered by the World Health Organization (WHO) as a priority and therefore, since 2001, global measures have been taken regarding its control, mainly through resistance monitoring, prescriber, health professional and wider public education as well as regulation on antibiotic promotion by the drug industry⁽¹²⁾.

In our study classification of UTIs was done as complicated and uncomplicated. Most of the patients had complicated UTIs.

In our research sample only one type of microorganism was identified in order to avoid cofounders. In our research work we found E. coli and K. pneumoniae, the two most common UTIs causative agents. These findings are similar to other research studies. Our drug susceptibility results were also categorized on the basis of different OPDs and the ER, and it was found that the urine samples from all OPDs were about equally susceptible to the drug Fosfomycin, while the results of susceptibilities to nitrofurantoin were quite different in all of the OPD and the ER. UTI empirical therapy should be based on the knowledge of major involved microbial agents and on their antimicrobial sensitivity profile⁽¹²⁾. E.coli showed high sensitivity percentage to Fosfomycin (96.6%) which, according to the Portuguese Health Directorate General,⁽¹³⁾ allows for an efficient empirical use of this antibiotic .

In this research work, most cases were identified as complicated UTIs patients which was associated with male gender and DM. Our study found that Fosfomycin had higher efficacy for

inhibition of uropathogen in outpatients of PAEC General Hospital. Fosfomycin is most active drug against *E. coli*, and minimum inhibitory concentrations are typically low⁽¹⁴⁾. Other urinary microorganisms have variable susceptibility⁽¹⁵⁾. Fosfomycin has a bactericidal activity against gram-negative pathogens and some gram-positive pathogens. It is taken by either IV form or oral form in order to treat the infection. However, the antibiotic Fosfomycin is more expensive as compared to nitrofurantoin. It is recommended to mix the drug Fosfomycin with water in oral form. Fosfomycin is a safe and effective antibacterial drug for the treatment of UTIs. Nitrofurantoin is suitable treatment drug for uncomplicated lower UTIs. And is recommended a preferred drug in the international consensus guidelines in 2010⁽⁶⁾.

CONCLUSION

The most common uropathogen in patients suffering from UTIs was *E. coli* (70.1%), followed by *K. pneumoniae* (15.5%). The susceptibilities of both the drugs are high as compared to other antibiotics. Fosfomycin is a safe and effective antibacterial drug for the treatment of UTIs. Nitrofurantoin is suitable drug for uncomplicated lower UTIs.

REFERENCES

- Hanley J, Branford I, Gugnani H, Wilkinson C, Uhrin T. Urinary bacterial pathogens and their antimicrobial susceptibility profile for the years 2005-2007 in St Kitts. *West Indian Medical Journal*. 2009;58(6):571-4.
- Jones TC, Hard GC, Mohr U. *Urinary system*: Springer Science & Business Media; 2013.
- Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *The American journal of medicine*. 2002;113(1):14-9.
- Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clinical therapeutics*. 1999;21(11):1864-72.
- Hendlin D, Stapley E, Jackson M, Wallick H, Miller A, Wolf F, et al. Phosphonomycin, a new antibiotic produced by strains of *Streptomyces*. *Science*. 1969;166(3901):122-3.
- Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical infectious diseases*. 2011;52(5):e103-e20.
- Grude N, Potaturkina-Nesterova N, Jenkins A, Strand L, Nowrouzian F, Nyhus J, et al. A comparison of phylogenetic group, virulence factors and antibiotic resistance in Russian and Norwegian isolates of *Escherichia coli* from urinary tract infection. *Clinical microbiology and infection*. 2007;13(2):208-11.
- Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of *Escherichia coli* from community-acquired urinary tract infections in Europe: the ECO-SENS study revisited. *International journal of antimicrobial agents*. 2012;39(1):45-51.
- Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clinical Infectious Diseases*. 1999;29(4):745-59.
- Seitz M, Stief C, Waidelich R. Local epidemiology and resistance profiles in acute uncomplicated cystitis (AUC) in women: a prospective cohort study in an urban urological ambulatory setting. *BMC infectious diseases*. 2017;17(1):685.
- Raz R. Fosfomycin: an old—new antibiotic. *Clinical microbiology and infection*. 2012;18(1):4-7.
- Garcia-Fulgueiras, V., Caiata, L., Bado, I., Giachetto, G., & Robino, L. (2022). Antibiotic susceptibility and fosfomycin resistance characterization in a cohort of children older than 6 years of age with urinary tract infection. *Revista Argentina de Microbiología*, 54(2), 120-124.
- Caskurlu, H., Culpan, M., Erol, B., Turan, T., Vahaboglu, H., & Caskurlu, T. (2020). Changes in antimicrobial resistance of urinary tract infections in adult patients over a 5-year period. *Urologia Internationalis*, 104(3-4), 287-292.
- Tutone, M., Johansen, T. E. B., Cai, T., Mushtaq, S., & Livermore, D. M. (2022). Susceptibility and Resistance to Fosfomycin and other antimicrobial agents among pathogens causing lower urinary tract infections: findings of the SURF study. *International Journal of Antimicrobial Agents*, 59(5), 106574.