ORIGINAL ARTICLE

COMPARISON OF SUSCEPTIBILITY BETWEEN CONVENTIONAL FIRST LINE ANTIBIOTIC CO-TRIMOXAZOLE AND NEWER ANTIBIOTICS IN RECURRENT UNCOMPLICATED URINARY TRACT INFECTIONS

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ABSTRACT

Objective: The current study aims to evaluate the susceptibility pattern of relatively older antibiotic Co-trimoxazole and its comparison with Levofloxacin, Nitrofurantoin, and Fosfomycin.

Material and Methods: This cross-sectional study was conducted in Mardan Medical Complex, Mardan, and the Postgraduate Medical Education Department of Khyber Girls Medical College, Peshawar from April 2022 to September 2022. Both male and female patients, above the age of 15 years with recurrent uncomplicated urinary tract infections were included in the study. The samples were inoculated onto CLED (Cystine-Lactose-Electrolyte-Deficient) Agar, a differential culture medium. The grown bacteria were identified, using Gram staining and BIOMÉRIEUX® API® 10S kits. Minimum inhibitory concentrations (MIC) were determined by the Agar dilution method; as per standard protocol. The results were compared among Co-trimoxazole, Levofloxacin, Nitrofurantoin, and Fosfomycin using statistical tests.

Results: A total of 680 samples were received, of which 158 samples were culture-positive. The gender distribution of females and males was 63.3% and 36.7%, respectively. A predominant proportion of the patient cohort manifested within the age range of 21-40 years, with the subsequent highest representation observed in the 41-60 year age group. The isolated organisms were E. coli (74.1%), Klebsiella (10.8%), Pseudomonas (5.1%), Enterococci (6.3%), Proteus species (2.5%), and Citrobacter (1.3%). Based on MIC analysis, 77.2% of isolates were found to be sensitive to Co-trimoxazole, 52.5% to Levofloxacin, 86.7% to Nitrofurantoin, and 90.5% to Fosfomycin. When comparing antibiotics, Co-trimoxazole displayed significantly higher effectiveness against the isolates compared to Levofloxacin (p-value 0.004). However, in comparison to Nitrofurantoin and Fosfomycin, Co-trimoxazole exhibited lower effectiveness, with respective p-values of 0.000 and 0.007.

Conclusion: The study revealed that the susceptibility of bacterial isolates to Co-trimoxazole is significantly higher than that to Levofloxacin but lower than that to Nitrofurantoin and Fosfomycin.

KEYWORDS: Urinary Tract Infections, Drug Resistance, Culture And Sensitivity, Minimum Inhibitory Concentration

This article may be cited as: Qadir H, Suleman S, Falah SF, Faisal MS, Sadia H, Ullah K. Comparison of Susceptibility between Conventional First Line Antibiotic Co-Trimoxazole and Newer Antibiotics in Recurrent Uncomplicated Urinary Tract Infections. J Med Sci 2023 October;31(4):309-314

INTRODUCTION

The discovery of penicillin in the 20th century marked the beginning of the antibiotic era which made a significant contribution to the decline in the rates of morbidity and mortality brought on by previously lethal illnesses. [1] The primary mortality shifted from infectious diseases to cardiovascular disease, stroke, and cancers in the United States (U.S.), while the average life expectancy at birth climbed to 78.8 years, and the senior population increased from 4% to 13%. [2] Unfortunately, the vast benefits of having access to antibiotic therapy are threatened by the rise of resistance in healthcare settings and the general population. [3] Currently, we are battling resistant strains causing infections most of which are essentially incurable. [4] Almost 17 million people die from bacterial infections each year. Infectious diseases are now the second leading killer in the world, third in developed countries, and fourth in the U.S. [5] Antibiotic resistance poses a serious risk to global

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Date Received: 08-07-2023
Date Revised: 01-09-2023
Date Accepted: 09-09-2023

mortality and economic burden. The widespread misuse of antibiotics, non-human antibiotic use, poor drug quality, inadequate surveillance, and aspects of individual and societal poverty (poor healthcare standards, malnutrition, chronic and recurrent infections, unaffordability of more expensive and effective drugs) have a more significant impact on developing nations. Furthermore, it is essential to address the scarcity of novel medications and manage resistance effectively to prevent the exhaustion of strategies countering it. [6] Antibiotic resistance in urinary tract infections has been rising in a variety of contexts and is linked to worse outcomes, such as symptom persistence, repeated doctor visits, and disease progression brought on by ascending infection. [7, 8] UTIs, without any anatomical or functional abnormality are categorized as uncomplicated urinary tract infections (uUTIs). When at least three UTI episodes occur within 12 months or at least two episodes occur within 6 months; it is labeled as Recurrent UTI (rUTI) which is challenging to manage. [9-11]

Drug discovery, resistance monitoring, and combinations of novel approaches to decrease resistance are only a few of the measures that will ultimately be needed to control resistance. One component of the comprehensive approach can be a reuse of the old "forgotten" medications. [12,13] Co-trimoxazole is the combination of Trimethoprim (TMP) and Sulfamethoxazole (SMX), which was once a very commonly prescribed combination antibiotic with a better safety and efficacy profile. TMP and SMX both work by obstructing particular mechanisms that produce metabolically active folate.[14] Traditionally used as first-line treatment in the empirical management of uUTIs, Co-trimxazole is no longer regarded as first-line therapy because of reported resistance higher than 20%. However, this medication is still among the antibiotics that can be regularly used to treat UTIs.[15] Bacteria will inevitably adapt to therapies, therefore to stay ahead of the game, our techniques for dealing with resistance must also change. This study aimed to assess the antibacterial effectiveness of Co-trimoxazole and compare it with commonly prescribed antibiotics like Levofloxacin, Nitrofurantoin, and Fosfomycin. The fundamental approaches for assessing the susceptibility of bacteria to antibiotics are the Minimum Inhibitory Concentration (MIC) and the Disk diffusion methods. We chose MIC because it accurately measures the antibiotic concentration required to inhibit bacterial growth. This precision is particularly valuable when dealing with resistant bacterial strains, as it enables us to determine the exact susceptibility of these bacteria to antibiotics.

MATERIAL AND METHODS

The study was conducted in Mardan Medical Complex, Mardan, and the Postgraduate Medical Education Department of Khyber Girls Medical College, Peshawar, Pakistan. Ethical and institutional approvals were obtained from the review board of Khyber Medical University (No. DIR/KMU-AS&RB/CS/001660). A standardized proforma was filled from clinically diagnosed cases of recurrent uncomplicated UTI who were advised a urine culture and sensitivity test. Colonies from culture-positive samples were collected and stored for bacterial identification, antibiotic susceptibility, and MIC testing following the Clinical and Laboratory Standards Institute (CLSI) guidelines (M100-S31, M07-A9). [16, 17] The samples were inoculated onto CLED (Cysteine-Lactose-Electrolyte-Deficient Agar) and incubated at 37°C for 24 hours. The bacteria were identified by Gram staining and BIOMÉRIEUX® API® 10S kits. The basal media used for Agar dilution was Mueller-Hinton (MH) and was determined based on the type of organism. The pure antibiotic powder was sourced from a pharmaceutical company and stock solutions were prepared with concentrations of 1000μg/ml for Co-trimoxazole, 10μg/ml for Levofloxacin, 1020μg/ml for Nitrofurantoin and 1020μg/ml for Fosfomycin. Glucose 6 Phosphate at a concentration of 25mg/L was also added to the agar for Fosfomycin. Five serial dilutions of different concentrations were prepared for each antibiotic. For every stored sample, fresh sub-cultures were grown on CLED media. Colonies of bacteria were inoculated in distilled water (5ml) and the turbidity was adjusted to 0.5 McFarland Standard. Starting from the lowest concentrations, 2µl of inoculum was placed on properly labeled specific areas of agar plates. The plates were allowed to set at room temperature until the inoculum spots were dry, followed by incubation at 37°C for 18-24 hours. Following the incubation period, the Minimum Inhibitory Concentration (MIC) was determined as the antibiotic concentration at which the growth of an isolate was arrested, and no discernible presence of a faint haze or the growth of a solitary colony was detected (Figure 1). The growths were also cross-checked with the control plates. For statistical analysis of comparison among susceptibilities of isolates, the chi-square test was applied.

RESULTS

In the Microbiology laboratory of Mardan Medical Complex, a total of 680 samples were received, of which 158 samples tested positive for bacterial culture. Among the individuals included in the study, 100 (63.3%) were females, and prevalent bacterial isolates from this group included E. coli, Klebsiella, and Proteus species. Moreover, 58 individuals (36.7%) were males, and the most commonly isolated bacteria from this group were Pseudomonas, Enterococci, and Citrobacter. E. coli emerged as the predominant organism, accounting for 74% of the isolates, followed by Klebsiella, Enterococci, Pseudomonas, Proteus species, and Citrobacter, as illustrated in Figure 2.

Against the isolated organisms, Co-trimoxazole displayed MIC values of 40μg/ml (77.2%), 80μg/ml (10.8%), and 100μg/ml (12%). Levofloxacin exhibited MIC values of 0.5μg/ml (50.6%), 1μg/ml (1.9%), 2μg/ml (27.2%), and 4μg/ml (20.3%). Nitrofurantoin had MIC values of 32μg/ml (84.8%), 64μg/ml (1.9%), and 128μg/ml (13.3%). Fosfo-

mycin showed MIC values of 64μg/ml (89.9%), 128μg/ml (0.6%), and 256μg/ml (9.5%), as depicted in Table 1. For the purpose of statistical comparison, intermediate sensitivity was also considered as sensitive, while all concentrations classified as resistant to isolates were included in the resistant group, as represented in Table 2.

When comparing Co-trimoxazole to Levofloxacin, a total of 72 isolates were sensitive while 25 isolates were resistant to both antibiotics. The sensitivity to Co-trimoxazole was significantly higher than that of Levofloxacin, with a p-value of 0.004. In comparison with Nitrofurantoin, 113 isolates were sensitive and 12 isolates were resistant to both antibiotics, with a p-value of 0.000. Similarly, when comparing Co-trimoxazole to Fosfomycin, 115 isolates were sensitive and 8 were resistant to both with a p-value of 0.007. It is worth noting that the sensitivity was significantly higher for Nitrofurantoin and Fosfomycin compared to Co-trimoxazole. Further details can be found in Table 3.

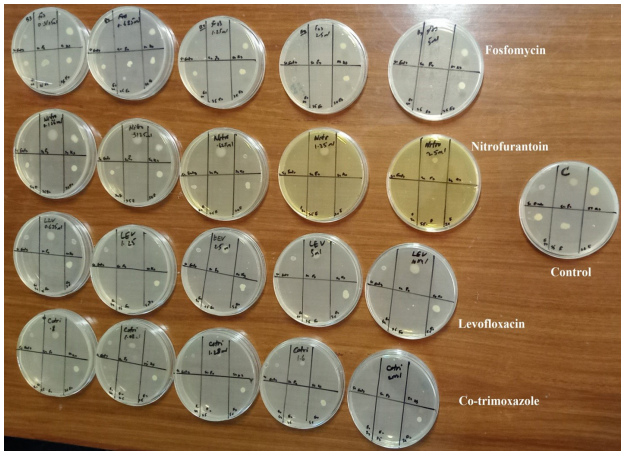

Fig 1: Showing Agar plates of Co-trimoxazole, Levofloxacin, Nitrofurantoin, and Fosfomycin. The plates are labeled with concentrations and types of bacteria. The growth of colonies can be seen at different concentrations and control plates after incubation for 18-24 hours at 37°C.

DISCUSSION

In empiric antibiotic therapy, treatment choices are educated guesses based on the relative frequency of the bacteria causing the infection and their rates of resistance. Guidelines for empiric antibiotic therapy take into account the severity of the infection as well as the selection of the most effective drug. In the current study, the MIC agar dilution method revealed that 77.2% of the isolates were sensitive to Co-trimoxazole at a concentration of 40μg/ml, while concentrations of 80μg/ml and higher were associated with a resistance rate of 22.6%. This type of susceptibility pattern has also been identified in a meta-analysis in Korea that concluded almost 40% resistance to Co-tri-

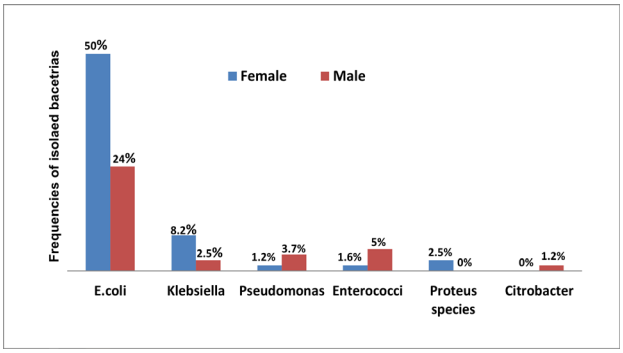

Fig 2: Organisms isolated from study samples with gender-wise distribution. Escherichia coli (E. coli), Klebsiella pneumonia (klebsiella), Pseudomonas aeruginosa (pseudomonas), Enterococcus Species (enterococci), Proteus species and Citrobacter

Table 1: Susceptibility pattern of selected antibiotics at various MIC

Class of Antibiotic	Antibiotic	MIC	Susceptibility	N (%)
Folate pathway inhibitors	Co-trimoxazole	40	S	122 (77.2)
		80	R	17 (10.8)
		100	R	19 (12)
Fluoroquinolones	Levofloxacin	0.5	S	80 (50.6)
		1	IS*	3 (1.9)
		2	R	43 (27.2)
		4	R	32 (20.3)
Nitrofurans	Nitrofurantoin	32	S	134 (84.8)
		64	IS*	3 (1.9)
		128	R	21 (13.3)
Phosphonic acid derivative	Fosfomycin	64	S	142 (89.9)
		128	IS*	1 (0.6)
		256	R	15 (9.5)

*The intermediate sensitivity was considered as sensitive

MIC-Minimum Inhibitory Concentration, S-Sensitive, IS-Intermediate Sensitive, R-Resistant

MIC is measured in μg/ml; Numerical values are expressed in frequencies and percentages

Table 2: Susceptibility pattern of bacterial isolates

Antibiotics	Susceptibility N (%)	
	Sensitive	Resistant
Levofloxacin	83 (52.5)	75 (47.5)
Co-trimoxazole	122 (77.2)	36 (22.8)
Nitrofurantoin	137 (86.7)	21 (13.3)
Fosfomycin	143 (90.5)	15 (9.5)

Numerical values are expressed in frequencies and percentages

Table 3: Comparison between effectiveness of study antibiotics and Co-trimoxazole

Study antibiotics		Co-trimoxazole		Total	X2	p-value*
		Sensitive	Resistant			
Levofloxacin	Sensitive	72	11	83	9.0	0.004
	Resistant	50	25	75		
Nitrofurantoin	Sensitive	113	24	137	16.25	0.000
	Resistant	9	12	21		
Fosfomycin	Sensitive	115	28	143	8.791	0.007
	Resistant	7	8	15		

*Calculated by Chi-square

Numerical values are expressed in frequencies

moxazole but also reported a significant decrease in rates of resistance per year. [18]

Another study reported susceptibility rates of 72.9% for E. coli and 89.8% for Klebsiella to Co-trimoxazole, which is consistent with our findings. [19] However, a meta-analysis conducted in Iran reported a Co-trimoxazole resistance rate of 64%, which contrasts with our findings. [20] The sensitivity pattern of Levofloxacin (50.6%) is similar to a study that found sensitivities of 64.5% and 47.9% for species such as E. coli and Klebsiella, respectively. [21]

The MIC at which Levofloxacin exhibited resistance was 2μg/ml and higher, affecting a total of 47.5% of the reported organisms. An Egyptian study reported similarly elevated rates of Levofloxacin resistance in E. coli (56.34%) and Klebsiella (86.2%). However, studies conducted in other parts of the world reported very high susceptibility of bacteria to Levofloxacin, such as 94.7% in Yemen and 85% in Libya. [22-24] Drugs like Nitrofurantoin and Fosfomycin are now considered the first-line treatment options for uncomplicated urinary tract infections. [9, 13] In the current study, Nitrofurantoin displayed 84.8% sensitivity at a concentration of 32μg/ml, while 13.9% of organisms were resistant at a concentration of 128μg/ml. Similar findings were reported in Bangladesh showing 16.10% resistance to E. coli and 75% susceptibility to species like pseudomonas. Contrary to this, an Indian study reported a lower susceptibility of 62% to Nitrofurantoin. [25, 26]

Our observation of 89.9% sensitivity to Fosfomycin at a concentration of 64μg/ml aligns with the findings of many studies reporting variable sensitivities ranging from 86% to 95% and cure rates of up to 90% in UTIs caused by E. coli. [27, 28] Despite higher rates of susceptibility to Nitrofurantoin and Fosfomycin, the therapeutic outcomes may differ among women with uncomplicated UTIs. A 5-day Nitrofurantoin regimen has a lesser chance of recurrent infection as compared to a single dose of Fosfomycin. [29] Keeping in view the resistance pattern of antibiotics in this study, the detection of resistant genes to Fosfomycin, Co-trimoxazole, Fluoroquinolones, and Nitrofurantoin should be taken into consideration as suggested in many studies.[30-32]

The findings from a study conducted in 2021, which reported susceptibility rates of 24%, 24.4%, 35.6%, and 45.8% for Levofloxacin, Co-trimoxazole, Nitrofurantoin, and Fosfomycin, respectively, align with our recommendation to prioritize Co-trimoxazole over Levofloxacin, but not over nitrofurantoin and fosfomycin. Co-trimoxazole has shown promising results in treating UTIs in areas where resistance is more than 20% but it is still not recommended as First-line empiric therapy for recurrent uncomplicated UTIs. [18, 32-35]

CONCLUSION

In our study cohort, the bacterial isolates showed appreciably higher susceptibility to Co-trimoxazole compared to Levofloxacin (a Fluoroquinolone). However, it remained inferior to the susceptibility rates observed for Nitrofurantoin and Fosfomycin. Given the guideline that antibiotics exhibiting resistance levels surpassing 20%

should be avoided for empirical therapy, the presence of a 22.8% resistance rate to Co-trimoxazole discourages its consideration as an empirical antibiotic option. However, it can be preferred over Levofloxacin in recurrent uncomplicated UTIs.

ACKNOWLEDGMENT

We are thankful to the laboratory staff of Mardan Medical Complex and Khyber Girls Medical College for providing technical support.

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CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE: NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Qadir H:	Data Collection, data analysis manuscript writing
Suleman S:	Concept, supervision
Falah SF:	Technical support, data analysis
Faisal MS:	Execution, manuscript writting
Sadia H:	Data Collection, statistical anaylsis
Ullah K:	Data Collection, data anaylsis

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.