

Fluoroquinolones Resistance to Esbl Positive Escherichia Coli Causing Urinary Tract Infection in Khyber Teaching Hospital Peshawar

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ABSTRACT

Objective: To find the resistance of fluoroquinolones to ESBL producing E. coli causing urinary tract infection.

Study Design: Single center observational study.

Place and Duration of Study: This study was conducted at the Department of Nephrology, Khyber Teaching Hospital Peshawar from September 2018 to February 2019.

Materials and Methods: Urine samples for culture and sensitivity were collected from patients having UTI. Urine cultures for ESBL positive E. coli were included in the study. We analyzed the resistance of fluoroquinolones in ESBL positive E. coli in urinary tract infection.

Results: Total of 104 patients were included in the study. Male to female ratio was 1:1.47. Age range was 15 to more than 60 years. Resistance to norfloxacin, ciprofloxacin and levofloxacin was found to be 81.7%, 84.6% and 80.8% respectively.

Conclusion: The age group and the gender did not make any statistically significant difference in resistance pattern. There was more than 80% resistance to fluoroquinolones in ESBL positive E. coli urinary tract infection.

Key Words: fluoroquinolones resistance, ESBL positive E. coli, urinary tract infection.

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INTRODUCTION

Urinary tract infection (UTI) is considered as the fourth leading cause of infection with a very high consumption of medications¹. Many microorganisms are involved in the etiology of UTI including Staphylococcus aureus, Pseudomonas aeruginosa, proteus species and streptococcus species^{2,3}, but Escherichia coli is considered as the predominant cause, in 80% of urinary tract infections (UTI) worldwide⁴.

The prevalence of Multi-drug resistance species of micro-organisms upsurges recently with special concern about the gram-negative bacteria that produces extended spectrum β -lactamase (ESBL) and are resistant to many classes of drugs which are not limited to penicillin, cephalosporin, monobactams excluding carbapenems.

The ESBL is produced by bacteria of enterobacteriaceae family including E. coli^{4,5,6}.

The fluoroquinolones are a group of antibacterials with major clinical importance, being one of the most frequently prescribed classes of antimicrobial agents in the world especially for UTIs because of their availability in both oral and intravenous forms. Resistance to fluoroquinolones emerges recently due to the intensive use of these drugs worldwide and is high in developing countries due to poor hygiene, illiteracy and poverty. Furthermore, fake and spurious drugs are also prevalent in the surroundings that attract patients because of low cost. Self-medication and easy availability of drugs without prescription is also common in the developing countries⁷.

The recent guidelines recommend the reservation of fluoroquinolones to severe and resistant infections and need to be prescribed following proper antimicrobial susceptibility testing to identify microorganism involved⁸.

The prescription of fluoroquinolones for UTI is very high with limited data availability on its resistance in our population. The aim of this study is to know about the resistance of fluoroquinolones in ESBL producing E. coli in patients with UTI in the department of nephrology Khyber Teaching Hospital Peshawar Pakistan irrespective of their disease status.

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MATERIALS AND METHODS

A single-center cross-sectional study was carried out to meet the objective of the study. This study was conducted in the department of nephrology, Khyber Teaching Hospital Peshawar. Urine samples for culture and sensitivity were collected from the patients having UTI from Sept 2018- Feb 2019. A mid-stream urine sample was collected in pre-sterilized container. For catheterized patients, urine sample was collected using sterile syringe after washing the tip of the catheter with boric acid. The collected samples were inoculated on MacConkey agar medium and incubated for 24-48 hours. Antibiotic susceptibility test was done using the Kirby-Bauer disk diffusion method that is based on the Clinical and Laboratory Standards Institute (CLSI)⁹. The commercially available antibiotic discs including ciprofloxacin, levofloxacin and norfloxacin were used. E. coli ATCC 25922 was used as a control organism. Double disc method following CLSI guidelines for confirmation of ESBL was used. An increase in zone of inhibition (5-12mm) for ceftriaxone and/or ceftazidime and/or cefotaxime confirmed the production of ESBL^{10,11}. Total 104 confirmed ESBL E.coli samples were included in the study. The data was analyzed using SPSS version 20.0. All the numerical data was expressed as Mean ± standard deviation (SD). The chi-square test was used for categorical data with p value <0.05 was considered significant. The graph was constructed using graphed Prism version 7.0.

RESULTS

In all 104 patients, 42 (40.4%) were males while 62 (59.6%) were females. Resistance to norfloxacin, ciprofloxacin and levofloxacin was found to be 81.7%, 84.6% and 80.8% respectively, while these drugs were sensitive only to 19(18.3%), 16(15.4%) and 20(19.2%) cases as shown in table 1. The age group were categorized as group 1, 2, 3 and 4. Group 1 includes patients which age range from 15-30 years, group 2 age range is from 31-45 years, group 3 age range is from 46-60 years and group 4 age range is above 60 years graphically presented in figure 1. The number of patients in group 1, 2, 3 and 4 are 16, 22, 30 and 33 respectively.

Table No.1: frequency distribution

Variables		Frequency	% age
Gender	Male	42	40.4
	Female	62	59.6
Norfloxacin	Sensitive	19	18.3
	Resistant	85	81.7
Ciprofloxacin	Sensitive	16	15.4
	Resistant	88	84.6
Levofloxacin	Sensitive	20	19.2
	Resistant	84	80.8

Table No.2: Association of Gender with resistance pattern

	Sensitive	Resistant	X ² -value	p-value
Ciprofloxacin				
Males	7	35	0.08	0.78
Females	9	53		
Levofloxacin				
Males	8	34	0.002	1.0
Females	12	50		
Norfloxacin				
Males	7	35	0.12	0.80
Females	12	50		

Table No.3: Association of different age categories with resistance pattern

Ciprofloxacin				
Age Groups (years)	Sensitive	Resistant	X ² -value	p-value
Group 1 (15-30)	06	13	4.86	0.18
Group 2 (31-45)	02	20		
Group 3 (45-60)	04	26		
Group 4 (>60)	04	29		
Levofloxacin				
Group 1 (15-30)	06	13	5.2	0.15
Group 2 (31-45)	01	21		
Group 3 (45-60)	07	23		
Group 4 (>60)	06	27		
Norfloxacin				
Group 1 (15-30)	05	14	2.49	0.47
Group 2 (31-45)	03	19		
Group 3 (45-60)	07	23		
Group 4 (>60)	04	29		

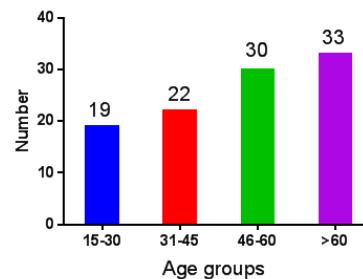


Figure No.1: UTIs cases in different age groups

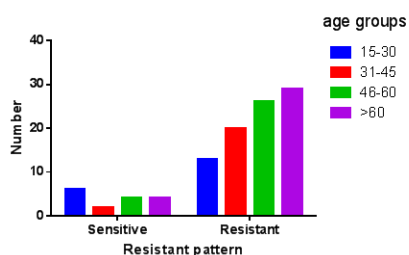


Figure No.2: Resistant pattern with age groups in number of patients.

DISCUSSION

Fluoroquinolones are the only broad-spectrum antimicrobial agents that target bacterial DNA thereby inhibiting two enzymes, DNA gyrase and topoisomerase IV. Resistance to quinolones develop by chromosomal genes mutation that encodes the DNA gyrase and topoisomerase IV leading to modifications in target site and membrane permeation channels. Several other mechanisms of resistance to quinolones have also been reported¹², and these occur due to multiple exposure of a patient to antimicrobial agents. Hospital acquired infections and admissions in intensive care unit are also associated with ESBL producing fluoroquinolone resistant UTI¹³. It has been reported that for one prescription of ciprofloxacin per month, the resistance was 3%, but with practices having 10 prescriptions per month resistance increased to 5.5%¹⁴. In Israel after restricting the use of Ciprofloxacin, resistance decreased from 12 % to 9%¹⁵. Fluoroquinolones are extensively used to treat UTI which is one of the most common bacterial infection that includes frequent relapses that may lead to pyelonephritis, kidney damage as well as complications caused by use of drugs for its eradication¹⁶. The emergence of ESBL mediated resistance in E.coli is alarming where the treatment option is very limited and is only sensitive to imipenem and meropenem but recently due extensive use of quinolones empirically, the resistance has increased¹⁷. In Our study resistance to norfloxacin, ciprofloxacin and levofloxacin to ESBL producing E.coli was 81.7%, 84.6% and 80.8%, respectively. This is similar to the study done six years back in our hospital looking for antibiotic susceptibility pattern to E.coli in UTI¹⁸. Our results show that gender doesn't make any difference in resistance pattern to norfloxacin (p value = 0.80), ciprofloxacin (p value = 0.78) and levofloxacin (p value = 1.0). Previous studies have shown that in E. coli UTI there was a lower incidence of resistance to fluoroquinolones in children as compared to adults and with increasing age the resistance to fluoroquinolones increased¹⁹. The same results were also shown in another study conducted in our hospital, showing resistance to fluoroquinolones upto 85% with increasing age¹⁸. Our study was about ESBL positive E.coli causing urinary tract infections the age

groups did not make any statistically significant difference to norfloxacin, ciprofloxacin and levofloxacin (table3).

A study published in 2001, reported 55.8% resistance to ESBL producing E.coli to 55.8% to fluoroquinolones¹⁷. Another study published in 2009 reported fluoroquinolones resistance to ESBL producing E.coli was 62.9%²⁰. In a study published in 2011, showed that 54% of the UTIs were caused by ESBL producing E. coli in which 85% were resistant to ciprofloxacin²¹. Jang WH et al have shown that E. coli resistance to levofloxacin was 29.49% by year 2005 which has increased to 43.2% by the year 2009²². According to the recent study published in 2019, 44% of the UTIs caused by E.coli of ESBL group shows 93.3% resistance to fluoroquinolones²³. WHO data from five regions reveal 50% resistance to fluoroquinolones in E.coli UTI²⁴.

The emergence of ESBL mediated E.coli is indeed a threat worldwide and especially to Pakistan where self-medication and misuse of antimicrobial agents is a major problem. A meta-analysis by Fasugba O et al showed that in Asia and Africa the pooled resistance was highest to ciprofloxacin compared to America and Europe¹⁹. The drugs can be directly purchased from the market without proper prescription which urges a proper policy in the country for the rational use and selling of drugs. In Countries having policies to control drug prescription, there's evidence of decline in use of antimicrobials and their resistance rates²⁵. Another reason for increase in antimicrobial resistance globally and specially in Asia is extensive use of antimicrobials in animal food²⁶. The health care providers must choose proper antimicrobial agent through authentic laboratory investigations rather than empirical treatment for these infections as well as public awareness is needed to discourage misuse and self-medication to limit antimicrobial resistance and health care burdens. New IDSA guidelines suggest using trimethoprim-sulphamethoxazole, nitrofurantoin and Fosfomycin as first line treatment for acute uncomplicated cystitis and advocate that fluoroquinolones should not be used for acute cystitis and can be reserved for complicated cases²⁷.

CONCLUSION

The prevalence of ESBL producing E.coli is increasing day by day therefore, decreasing the drug susceptibility and increasing resistance pattern. Fluoroquinolones should not be used as first line treatment in UTIs. The use of antibiotics in animal food for their growth should also be limited, as it has positive correlation with increasing resistance to antibiotics. New strategies need to be defined properly for prescribing as well as selling of these drugs to further limit the resistance patterns. Infection control units need to be developed in every tertiary care hospital to guide clinicians and health care

providers in selection of proper antimicrobial agents for specified infections.

Author's Contribution:

Concept & Design of Study: Shandana Altaf
 Drafting: Tayyaba Basharat
 Data Analysis: Mariana Amer, Waheed Iqbal, Amer Azhar
 Revisiting Critically: Shandana Altaf, Tayyaba Basharat
 Final Approval of version: Shandana Altaf

Conflict of Interest: The study has no conflict of interest to declare by any author.

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