

E. coli Resistance to Ciprofloxacin and Common Associated Factors

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ABSTRACT

Objective: To determine the frequency of *E. coli* resistance to ciprofloxacin and common factors leading to it among patients presenting with urinary tract infection.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Department of Medicine, Ayub Teaching Hospital, Abbottabad, from December 2011 to June 2012.

Methodology: A total of 166 patients, > 18 years of age of both gender, who presented with features of UTI and had urine culture positive for *E. coli* were included in the study. The urine samples were further tested for ciprofloxacin resistance and the patients were further checked for the common factors leading to *E. coli* resistance to ciprofloxacin.

Results: Among 166 patients, 41 were male and 125 were female patients. Sixty-six (39.8%) *E. coli* isolates showed ciprofloxacin resistance. Male gender (p-value 0.001), previous history of recurrent UTI (p = 0.008, OR = 2.37), history of prior use of ciprofloxacin (p = 0.018, OR = 2.16) and history of catheterization (p = 0.005, OR = 4.80) were independent risk factors found in this study for the development of ciprofloxacin resistant UTIs.

Conclusion: Ciprofloxacin resistance rates of *E. coli* were high at over 39.8%. The risk factors that affected the ciprofloxacin resistance rates of *E. coli* were prior use of ciprofloxacin, recurrent UTI, previous catheterization and male gender. Ciprofloxacin should be prescribed cautiously in patients with these risk factors and urine culture and sensitivity test should be performed for optimal treatment.

Key Words: Urinary tract infection. *E. coli*. Ciprofloxacin. Resistance.

INTRODUCTION

Urinary Tract Infection (UTI) is one of the most common presentations in the outpatient as well as in admitted patients.¹ UTI accounts for the most common bacterial infection, causing 150 million cases annually worldwide. The cost of managing it runs in billions of US dollars.²

The majority of UTIs are caused by *E. coli* in 75 - 90% of cases followed by *Staphylococcus saprophyticus*, mainly in younger women.²⁻⁴ Several studies have shown escalating levels of antibiotic resistance in *E. coli* causing UTI.⁵⁻⁸ Resistant pattern shows geographical variations.^{8,9} In Turkey 17% of *E. coli* strains isolated from uncomplicated cases and 38% of *E. coli* strains isolated from complicated UTI were found to be resistant to ciprofloxacin.⁵ The incidence of ciprofloxacin resistant *E. coli* has risen from 1.8% to 15.9% in the previous 10 years in Switzerland.⁶ In Pakistan, data on this subject is lacking. It is known that the *E. coli* is the most frequent (about 86.4%) uropathogen, and its resistance to ciprofloxacin is increasing, i.e. 27% in patients who had attended urology outpatient department with various urological problems and 72% in admitted patients.¹⁰

Factors associated with resistance to ciprofloxacin in *E. coli* reported in previous studies include old age, male gender, diabetes mellitus, urinary tract abnormalities, recurrent UTI, previous therapy with quinolones, urinary catheterization and presence of complicated UTI.^{6-8,11,12} There are only few studies, conducted in developed countries, that have analyzed demographic and epidemiological data to determine the risk factors associated with rising antibiotic resistance among uropathogens.¹¹

There is little data available about risk factors leading to antibiotic resistance in Pakistan and no data is available in recent time in our local population. Therefore, this study is planned to identify the frequency of *E. coli* resistance to ciprofloxacin and common factors leading to it among patients presenting with urinary tract infection. This study will provide us with local magnitude of the problem including the factors associated with it as mentioned above, there is geographical variation for *E. coli* resistance to ciprofloxacin. The results of the study is expected to provide useful information that would assist physicians in prescribing appropriate antibiotics, leading to a better management of urinary tract infections.

METHODOLOGY

It was a hospital-based descriptive cross-sectional study. Patients were included in the study who presented to the OPD of Ayub Teaching Hospital with

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urinary tract infection and culture yielding *E. coli* during the 6 months period from 26th December 2011 to 25th June 2012. Sample size was 166 keeping 8.7%¹² proportion of recurrent UTI as a factor leading to ciprofloxacin-resistant *E.coli*, 95% confidence interval and 4.3% margin of error using the WHO software (sample size determination in health studies). The sampling technique was non-probability consecutive sampling. Patients were of either gender and of age 18 years and above.

The study was conducted after approval from hospital ethical and research committee. The purpose and benefits of the study was explained to all patients and a written informed consent was obtained. Detailed history and clinical examination was performed and those patients with signs of pyelonephritis, pregnancy, immunocompromised states, psychiatric illness, drug addictions and connective tissue disorders were excluded from the study.

The urine specimens were collected in a sterile container, after instructing the patient about the sterile midstream urine collection technique. Patients' data was recorded and the urine samples were sent to the hospital's microbiology laboratory for urine culture and sensitivity. Each urine specimen was inoculated on both blood agar and MacConkey agar plates using a 0.01 mL standard loop and incubated aerobically at 37°C for 24 - 48 hours and the number of colonies were counted. The identification of *E.coli* was performed by minimal standard bacteriological tests, using conventional biochemical markers by the laboratory pathologist. Only those specimens having more than 10⁵ Colony Forming Units (CFU) of *E.coli* per milliliter of urine were further tested for ciprofloxacin resistance. *E.coli* resistance to ciprofloxacin was checked according to the Clinical and Laboratory Standards Institute (CLSI). In the disk diffusion test, ciprofloxacin zone diameters of < 21 mm was considered resistant.

Once detected, all the patients with ciprofloxacin resistance were further checked for the common factors leading to *E.coli* resistance to ciprofloxacin (diabetes mellitus, immunosuppressive drugs use, prior use of ciprofloxacin, recurrent UTI and history of urinary catheterization). All the data was recorded on a pre-designed proforma. A strict exclusion criterion was followed to control confounders and bias in the study results.

Data was analyzed using SPSS version 16.0. Numeric variables like age were described as mean ± SD. Frequency and percentages were calculated for categorical variables like gender, ciprofloxacin resistance to *E.coli* and common factors leading to it (diabetes mellitus, use of immunosuppressive agents, prior use of ciprofloxacin, recurrent UTI and history of urinary catheterization). Chi-square test was used for

statistical analysis. P-value and odds ratio were calculated for risk factors. A p-value of < 0.05 was considered statistically significant.

RESULTS

Urine samples from outpatients of age group 18 years and above were submitted to the microbiology laboratory. Only 166 patients who had urine culture positive for *E.coli* were included in this study. There were 41 (24.7%) male patients and 125 (75.3%) female patients in the study. The male to female ratio was 1:3.05. The mean age of the male patients was 53.24 ±10.25 years, and female patients was 45.75 ±14.94 years. There were 31 (18.7%) patients of age range of 18 - 30 years, 14 (8.4%) patients of age range of 31 - 40 years, 33 (19.9%) patients of age range of 41 - 50 years, 52 (31.3%) patients of age range of 51 - 60 years and 36 (21.7%) patients of age more than 60 years.

Among 166 patients presenting with UTI having *E.coli* as causative organism, 100 (60.2%) isolates were sensitive to ciprofloxacin whereas only 66 (39.8%) isolates were ciprofloxacin resistant.

Among 41 male patients, the urine culture and sensitivity test showed that 25 (61%) *E.coli* isolates were resistant to ciprofloxacin and 16 (39%) were found to be sensitive. And out of 125 female patients, only 41 (32.8%) of *E.coli* isolates were ciprofloxacin resistant and 84 (67.2%) were sensitive to ciprofloxacin. Thus with p-value of 0.001, male gender was a significant risk for ciprofloxacin resistance (Table I).

There were 56 (33.7%) patients who have previous history of recurrent UTI and among them 30 (53.6%) patients' urine culture and sensitivity test reports showed *E.coli* resistance to ciprofloxacin and 26 (46.4%) patients were sensitive (p = 0.008, odd ratio, OR = 2.37).

History of prior use of ciprofloxacin was present in 59 (36.1%) patients and among them 31 (51.7%) patients

Table I: Distribution of *E. coli* resistance to ciprofloxacin in relation with different gender and age groups.

Age groups	Gender	<i>E.coli</i> resistance to ciprofloxacin		Total (n) (%)
		Yes n (%)	No n (%)	
18 - 30	Male	1 (50)	1 (50)	2 (100)
	Female	3 (10.3)	26 (89.7)	29 (100)
	Total	4 (12.9)	27 (87.1)	31 (100)
31 - 40	Male	2 (60)	1 (40)	3 (100)
	Female	5 (35.7)	6 (64.3)	11 (100)
	Total	7 (39.4)	7 (60.6)	14 (100)
41 - 50	Male	3 (57.1)	2 (42.9)	5 (100)
	Female	10 (41.9)	18 (58.1)	28 (100)
	Total	13 (48.1)	19 (51.9)	33 (100)
51 - 60	Male	12 (57.1)	9 (42.9)	21 (100)
	Female	13 (41.9)	18 (58.1)	31 (100)
	Total	25 (48.1)	27 (51.9)	52 (100)
61 - 75	Male	7 (70)	3 (30)	10 (100)
	Female	10 (38.5)	16 (61.5)	26 (100)
	Total	17 (47.2)	19 (52.8)	36 (100)

Table II: Frequency of common factors in patients with UTI in relation with *E. coli* resistance to ciprofloxacin.

Risk factors	Ciprofloxacin resistance to <i>E. coli</i>		Odd ratio	p-value
	Yes n (%)	No n (%)		
Recurrent UTI	30 (53.6%)	26 (46.4%)	2.37	0.008
History of prior use of ciprofloxacin	31 (51.7%)	29 (48.3%)	2.16	0.018
Diabetes mellitus	17 (51.5%)	16 (48.5%)	1.82	0.123
Immuno-suppressive agent use	4 (33.3%)	8 (66.7%)	0.741	0.636
History of catheterization	11 (73.3%)	4 (26.7%)	4.80	0.005

had ciprofloxacin resistant *E. coli* isolates, ($p=0.018$, OR = 2.16). Among the 33 diabetic patients, only 17 (51.5%) diabetic patients were found to have ciprofloxacin-resistant *E. coli* ($p = 0.123$, OR = 1.82).

Among this study group, 12 (7.2%) UTI patients had history of immunosuppressive drug use and among them only 4 (33.3%) had ciprofloxacin resistance to *E. coli* ($p = 0.636$, OR = 0.741).

There were 15 (9%) patients who had positive history of catheterization and about 11 (73.3%) were harboring ciprofloxacin-resistant *E. coli* in their urine. Thus with the odd ratio of 4.80 ($p=0.005$), catheterization was found to be significantly related with ciprofloxacin resistance in *E. coli* isolates (Table II).

DISCUSSION

The aim of this study was to measure the frequency of emerging ciprofloxacin resistance in *E. coli* strains isolated from UTI patients treated by Department of Medicine in Ayub Teaching Hospital and it had also evaluated the frequency of common factors attributed in resistance development. The resistance to ciprofloxacin is of great concern because fluoroquinolones are being used as the first-line antibiotic therapy for UTIs in the last few years.

This analysis demonstrated that 39.8% of the population under study had urinary tract infections with ciprofloxacin resistant *E. coli*. Such rising levels of antibiotic resistance in *E. coli* causing UTI have been shown in several studies.⁵⁻⁸ *E. coli* resistance to ciprofloxacin was reported as 14.71 - 19.22% in Turkey, 27% in Switzerland and 0 - 14.7% in the ECO-SENS Project.^{5,7,13} In the USA, resistance to ciprofloxacin is relatively low but it has been gradually increasing. Sanchez *et al.* showed the greatest increases in *E. coli* resistance from 2000 to 2010 for ciprofloxacin (3% to 17.1%) among urinary isolates obtained from US outpatients.¹⁴ In India, Joshi *et al.* in 2011 showed that only 30.44% of *E. coli* isolates were resistant to ciprofloxacin.² Data from Pakistan also show that the ciprofloxacin resistance rates of *E. coli* are increasing.^{10,15,16} This study results of resistance to ciprofloxacin (39.8%) was higher than values reported

by Farooqi *et al.* (25% in 1997)¹⁵ but is comparatively less than values reported by Ahmad *et al.* (50%).¹⁶

Age and male gender have an influence on antimicrobial resistance rates, mainly with the fluoroquinolone group.⁵ Governado *et al.* showed that *E. coli* resistance rates for ampicillin, co-trimoxazole and ciprofloxacin were notably higher in the elder group (> 65 years) compared with the other group of women (≤ 65 years).¹⁷ In this study, the ciprofloxacin resistance rate was comparatively higher in male gender ($p = 0.001$).

Only few studies have reported the risk factors for developing infections due to ciprofloxacin-resistant *E. coli* in the community setting. In a study from Turkey, age over 50 years, ciprofloxacin use more than once in the last year, and the presence of complicated UTI were significantly associated with ciprofloxacin resistance.⁵ In another study in Switzerland, Quinolone use in the preceding year, urinary tract catheterization in the preceding year and recurrent UTIs were found to be independently associated with infections with a ciprofloxacin-resistant strain.⁷

In this study, it was found that male gender ($p = 0.001$), previous history of recurrent UTI ($p = 0.008$), history of prior use of ciprofloxacin ($p = 0.014$) and history of catheterization ($p = 0.005$) were independent risk factors for the development of ciprofloxacin resistant UTI. These results are similar to the previously mentioned studies. Our findings suggested that DM and history of immunosuppressive agent use were not associated with an increase in antimicrobial resistance.

As this study is done in a tertiary care hospital, our study population is not a true representative of community acquired UTI, as most of the community acquired UTIs are treated by general practitioners. A selection bias of patients presenting with more severe infections is likely because we mostly receive cases that are either not appropriately treated or have recurrent episodes. We only checked the resistance pattern of urinary *E. coli* isolates which represent about 75% of uropathogens. We excluded complicated UTIs but included male patients in this study that should also be excluded, as male gender is considered as complicated cases by many centers.

We recommend that a large multi-center study should be performed in order to fully analyze the sensitivity patterns of different uropathogens and most importantly to fully analyze the frequency of various risk factors for the development of resistance in our region. This will help to provide basis for local guidelines for empirical treatment of community acquired UTIs.

CONCLUSION

Resistance in urinary *E. coli* isolates for ciprofloxacin is rising, and it reflects the increased use of antimicrobial compounds. Prior use of ciprofloxacin, recurrent UTI,

previous catheterization and male gender were identified as independent risk factors for ciprofloxacin resistant UTI. In patients with one or more of the risks identified here, the empiric use of ciprofloxacin should be reconsidered and urine culture and sensitivity testing must be performed for optimal treatment.

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