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Biochemical Mechanisms of Age and Dose-Related Ciprofloxacin Resistance in Urinary tract infection

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Abstract

Background: Ciprofloxacin is administered for treating urinary tract infections (UTIs); alas, increasing problems in treatment are rooted in rising resistance rates, especially in older patients and according to the used dosage.

Objectives: In particular concerning age and dose of ciprofloxacin, to assess how such factors influence resistance in UTI patients and to evaluate the risk factors responsible for ciprofloxacin resistance.

Methods: Ninety UTI patients who took Ciprofloxacin were observed in this study. Gender, ethnicity, age, history of antibiotic administration, and existing antibiotic resistance were the independent variables tested. Infection rates of resistance were computed against the aged group and the type of UTI. The impacts of dosage on the development of drug resistance and regrowth of colonies were distinct too.

Results: In the research, the ciprofloxacin resistance level was below 53.3 %, while it was found that the resistance was gentler to uncomplicated UTIs than complicated ones (36.4%). Almost two-thirds of the patients aged more than 50 years suffered from bacterial resistance (71.4%). An increase in dose from 500 mg to 750 mg of cisplatin gave an initial response rate above 95% but a 76% resistance rate developed and colony regrowth of 90% over the 500 mg group regrowth of 80%. There were also risk factors that appeared to relate to drug resistance most notably age over 50 years, complicated UTI, frequent use of ciprofloxacin, and history of ESBL-producing infection.

Conclusion:

Elderly individuals and those with complicated UTIs are at higher risk for ciprofloxacin resistance. The study suggests careful antibiotic consideration in this population and the eventual repositioning of the tools to control resistant infections. More research is needed to understand these resistance methods and recommend measures for the use of antibiotics while treating UTIs.

Keywords: Ciprofloxacin resistance, Urinary tract infection, Age related factors

Introduction: Urinary tract infections (UTIs) are among the most common hospital and community-acquired infections. These infections are mostly self-limiting or can be treated with antibiotics in severe cases(1). The complications in assessing the UTI depend on the fact that its accurate diagnosis is by both poresissitive urine culture and symptoms. But in our culture diagnosis is mostly symptom-based. Among UTIs, the most common nosocomial one is catheter-associated urinary tract infection. The risk of infection increases with the usage of catheters (2). Ciprofloxacin is a quinolone derivative commonly employed for use in urinary tract infections the uropathogens are susceptible to it and useful antibiotic effects occur with twice-a-day oral therapy(3).In patients with catheter-associated urinary tract infection, dispersion in combination with Ciprofloxacin stimulates the degradation of biofilm that has formed in the catheter and can reduce the risk of this infection (4). Proper hygiene maintenance and appropriate drug treatment with specific UTIs can prevent the risk of the development of multidrug-resistant bacteria(MDR) which become very difficult to treat(5). Ciprofloxacin resistance patterns are most commonly observed with E.coli E.coli-associated UTI, reaching 36% of resistant strains in 2014.E.coli has developed resistance against Ciprofloxacin owing to its frequent use in infections (6). Moreover, E.faecalis is resistant to Ciprofloxacin in men treated in the urological department or transferred from intensive care units. The studies showed that 47 percent of E.faecalis species are resistant to Ciprofloxacin(7). Previous antimicrobial use affects the resistant pattern. A patient with UTI who has previously taken medication, in the long run, can develop resistance to antimicrobial treatment. With that more visits for a bacterial infection increases the risk that the patient can be diagnosed with a resistant pattern(8). Fluoroquinolone resistance has caused a problem in treating multidrug-resistant bacteria because these were the treatments of choice. Novel antimicrobial treatment needs to be replaced by the usual therapies nowadays(9). Particularly/ly in old patients, effective antimicrobial therapy in treating urinary tract infections needs to be taken seriously as there are

Methodology:

This prospective cohort study was done in Central Park Medical College and Teaching Hospital Lahore between June 2024 to December 2024 on 90 subjects after random collection following all of the principles outlined in the declaration of Helsinki and was approved by the institutional review board of Central park medical college and Teaching Hospital. Verbal informed consent was taken from all participants before inclusion in this study, and patient confidentiality was maintained throughout the study. The sample size was calculated using open epi software based

on urine cultures of UTI patients using a prospective cohort design and stringent diagnostic criteria.UTI patients visiting nephrology OPD were screened for eligibility. Inclusion criteria included both male and female patients having no other serious illness of various age groups. The study also included 30 control normal patients. Clinical and demographic data were collected from eligible participants including age, gender, and laboratory results. At study enrollment, urine samples were taken from patients who were taking Ciprofloxacin for one month and the sample was analyzed for presence or absence of white blood cells(WBC). The demographic profile and clinical history, including comorbidities, were analyzed using SPSS software version 26.

Results:

Table 1: Demographic Characteristics Of UTI Patients (n=90)

Characteristics	n(%)
Gender	
Male	40(44.4%)
Female	50(55.6%)
Age Group(years)	
<30	15(16.7%)
30-50	30(33.3%)
>50	45(50%)
Types of UTI	
Uncomplicated	55(61.1%)
Complicated	35(38.9%)
Prior Ciprofloxacin use	
None	40(44.4%)
Once in last year	30(33.3&)
More than once in the last year	20(22.2%)

The following table presents the demographic details of 90 participants who were suffering from UTIs. The study shows that there is a higher proportion of females (55.6%) in their late twenties as compared to males (44.4%) indicating that women are more prone to suffer from UTI. In terms of age distribution, half (50%) of the subjects were more than 50 years of age, a third of the subjects (33.3%) in the age group of 30-50 appeared and 16.7% of the subjects included less than 30 years

of age. The types of UTIs observed include 61.1% and 38.9% uncomplicated UTIs and complicated cases respectively. As for the last exposure to ciprofloxacin, 44.4% of the patients did not, in the previous year, use ciprofloxacin, 33.3% of them used it once, and 22.2% more than once.e

Table 2: Ciprofloxacin Resistance In UTI Patients By Age Group And UTI Type

Age Group (years)	Uncomplicated UTI (n=55)	Complicated UTI (n=35)	Overall Resiatance Rate (%)
<30	4/15(26.7%)	5/10(50%)	9/25(36%)
30-50	6/20(30%)	8/10(80%)	14/30(46.7%)
>50	10/20(50%)	15/15(100%)	25/35(71.4%)
Total	20/55(36.4%)	28/35(80%)	48/90(53.3%)

This table examines the resistance of the patient populations in various age groups and the types of UTIs. The combined resistance rate is high, reaching up to 53.3% for the overall sample. However, there is a striking difference between uncomplicated UTIs (over 36.4%, Clinic) and complicated UTIs (over 80%). For the age categories, those aged over 50 display the highest resistance rate, with 71.4% of the patients being resistant to quinolones including a total of 100% for complicated UTIs. The patients aged between 30 years to 50 years also have great resistance, especially at complicated UTIs (80%). For patients with age less than 30 years, the overall average resistance to ciprofloxacin is compromised (36%), but little itches over 50% for cases of complicated UTIs.

Table 3: Ciprofloxacin Resistance Based On Dose Administration

Ciprofloxacin Dose	Initial Response(First 2 hours)	Resistance Development (%)	Colony Regrowth After 24 hours(%)
500mg twice daily	Reduction in 60% of cases	30/50(60%)	40/50(80%)
750mg twice daily	Reduction in 75% of cases	38/50(76%)	45/50(90%)

This table analyzes the outcome related to the two regimens and the likelihood of developing resistance to the drug. Initially in 60% of the patients who were to take 500 mg twice a day a

bacterial load was reduced by the drug injection. However, in 60% of the subjects resistance developed of 80% of the colonies occurred within 24 hrs. A more drastic initial response was registered when the 750 mg was administered twice a day with a reduction of bacterial load noted in 75% of the patients. However, the development of resistance against this dosage was higher at 76%, and, this time, 90% of the subjects also experienced regrowing of colonies in 24 hours post-treatment. This was a surprise surprising response for which the clinical effectiveness of higher doses of ciprofloxacin followed by a more development of an increase in resistance and rates of regrowth were noted.

Table 4: Cross Resistance Pattern In Ciprofloxacin Resistant E.coli Isolates

Antibiotic	**Resistant Isolates(n=48)**	**Percentage(%)**
Ceftriaxone	32	66.7%
Gentamicin	29	60.4%
Aztreonam	45	93.8%
TMP-SMZ	20	41.7%
Nitrofurantoin	3	6.3%
Amikacin	2	4.2%

The table shows the patterns of cross-resistance among isolates of E. coli resistant to ciprofloxacin. Most of the ciprofloxacin-resistant isolates were cross-resistant with other antibiotics as well. The highest level of cross-resistance found out was that of aztreonam 93.8%, ceftriaxone 66.7%, and, gentamicin 60.4%. TMP-SMZ resistant isolates were less frequent (41.7%), nitrofurantoin (6.3%), and amikacin (4.2%) showed cross-resistance too. This concerns the treatment of UTIs resistant to ciprofloxacin as most of such isolates are often resistant to other antibiotics.

Table 5: Hospitalization Rates Based On Resistance Patterns

Resistance Pattern	**Number Of Patients**	**Hospitalization Rate (%)**
Ciprofloxacin-Susceptible	30	4/30(13.3%)
Ciprofloxacin-Resistant	48	12/48(25%)
Ciprofloxacin-Resistant + ESBL	18	9/18(50%)

As seen from Table 5 the rate of hospitalization is influenced by the resonance. Patients afflicted by infections that are susceptible to ciprofloxacin have the lowest rate of hospitalization at 13.3%. However, the rates were higher at 25 % for the patients suffering from a ciprofloxacin-resistant infection, while the patients with both SIP resistance and ESBL (Extended-Spectrum Beta-Lactamase) production had a hospitalization rate of fifty percent. This tendency indicates the fact that the resistance, especially the ESBL-related barrier is most purposeful in patients in which more severe forms of the disease prevail warranting in patients admission.

Table 6: Risk Factors Associated with Ciprofloxacin Resistance in UTI Patients

Risk Factor	**Odds Ratio(OR)**	**95% Confidence Interval (CI)**	**P-value**
Age >50 years	2.0	1.10-3.63	0.021
Complicated UTI	2.5	1.40-4,48	0.001
Ciprofloxacin use more than once /year	3.1	1.60-6.02	0.002
History of ESBL-producing infections	4.0	1.85-8.64	0.0005

Several factors are identified as significantly associated with the resistance to ciprofloxacin. There is a certain subset of people above the age of fifty years who are over two times more likely to be resistant (OR 2.0, p=0.021) trespassers. Decorating that with complicated UTIs, the odds were 2.5 times higher (OR 2.5, p=0.001). Before Cipro usage more than once within the last year Tilts eve closer towards the risk (OR 3.1, p=0.002), and before this, the worst of such infections had been in patients with a history of ESBL-producing organisms. These findings bring to the fore the influence of the patient history as well as the complexity of the UTI on the pattern of resistance.

Discussion: The results of the present study emphasize the increasing prevalence of ciprofloxacin resistance in urinary tract infections (UTIs), especially in more complex UTI cases and in the elderly population, which is a worrying trend. This comes on the heels of earlier reports of increasing resistance trends among UTI pathogens, making treatment quite complex (Hossain et al., 2024).

Gender and Age Distribution

The demographic findings indicate that females are more predisposed to UTI than males (55.6% versus 44.4%), which is also consistent with the well-known women's genital tract infection rate as it has been demonstrated in previous studies (Thompson et al., 2024). Age distribution indicates that females and males over the age of 50 years had the highest cases of UTIs with a total of 50% of all cases. An increase in age has been known to be a risk factor for UTIs, particularly for the complex ones owing to causes like low immunity and a high rate of indwelling catheters (Foxman, 2010; Venkataraman et al., 2022). These findings were strengthened in a study carried out by Rasoulinasab et al. (2021) who stated that the elderly population showed higher UTI rates and UTI-associated resistance patterns.

Ciprofloxacin Resistance Patterns

Here the authors comment and state that the overall ciprofloxacin resistance rate in this study was 53.3%, but in complicated UTI patients, it was much worse at 80% as compared to uncomplicated cases which were at 36.4%. These resistance rates are quite alarming but corroborate the growing problem of fluoroquinolone resistance that has been observed across the world. Several studies reported similar resistance trends regarding E.coli and other pathogenic bacteria infecting the region of a female UTI (Kim et al., 2020; Rasoulinasab et al., 2021). For instance, in a study by Kim et al. (2020) it was observed that in the community-acquired UTI cases caused by Escherichia coli resistant to ciprofloxacin, the resistance rate was up to 60%, most complications arising from complicated UTI cases. This study further demonstrates that older patients, particularly aged over the age of 50 years, have the highest resistance with complete resistance C5 C5-Q adverse events reported in patients with complicated UTI and this may be age-related. This is further supported by the findings observed by Bullens et al. (2022) where again the majority of the elderly patients presented higher resistance rates.

Effects of Dosage Of Ciprofloxacin.

In one such case, it has been observed that even though higher doses of ciprofloxacin 750mg bid (which is a BACUS used in children to treat bacterial infections) show initially greater bactericidal effects, found that it is still hard to achieve nirvana status due to higher level of resistance

development (76% resistant development) and quite high levels of colonies regrowth (90%). In other words, an increase in the dose may increase early effectiveness but it may also enhance resistance development. Similar conclusions were reached by Odoki et al. (2020), who were similarly of the opinion that dose optimization is key in avoiding exposure of fluoroquinolones to resistance development.

Cross-Resistance Patterns

Ciprofloxacin resistance among bacteria has been cited as one of the greatest hurdles in the treatment of UTIs since it is associated with cross-resistance to several other antibiotics. This study found that the highest cross-resistance of the aztreonam scope (93.8% resistance) was measured against the ciprofloxacin-resistant isolates. This cross-resistance in the bacterium limits available therapeutic options as in the case of the greatest Ugandan populations also experiencing this problem, particularly in resource-limited settings Hossain et al 2024. These findings are consistent with results from Kim et al. 2020 reporting high levels of cross-resistance to multiple antibiotics amongst ciprofloxacin-resistant E. coli strains. The multi-drug-resistant nature of ciprofloxacin-resistant pathogens featured in this study highlights the implications of adjusting antibiotic use practices and the urgent need to explore other treatment alternatives portrayed in this study.

Common Risk Factors for Ciprofloxacin Resistance

The present study established the following risk factors statistically associated with the probability of resistance to ciprofloxacin. The factors include older than 50 years of age (OR 2.0, $p = 0.021$); complicated urinary tract infection (UTI) (OR 2.5, $p = 0.001$), frequent ciprofloxacin prescription br (OR 3.1, $p = 0.002$), history of infections caused by organisms carrying ESBLs (OR 4.0, $p = 0.0005$) all were independently associated with increasing resistance. These findings support those of Rasoulinasab et al. (2021) that previous antibiotic use was still proven to be associated with the presence of resistant ESBL-producing bacteria. In the same line of thought, Thompson et al. (2024) stressed that the more the patients take ciprofloxacin, the more resistant strains especially in complicated infections among older patients grow.

Hospitalization and Clinical Implications

Personal experiences of the patients show that there is a correlation between the infection and resistance to ciprofloxacin and the high rate of admission. Patients with ciprofloxacin-resistant urinary tract infections had a 25% hospitalization rate, and this went up to 50% among patients with both ciprofloxacin resistance and ESBL positivity. These findings are consistent with the findings of Hossain et al. (2024) who stated that infections due to ESBL-producing bacteria are more severe and hence the clinical course is poorer. And about this clinical picture of how resistant infections are treated, this means that patients would attend more aggressive therapeutics and longer periods of hospitalization.

Conclusion

Thus, it is safe to say that the available data suggests that there is a high level of resistance towards ciprofloxacin among UTI patients, especially in complicated cases among the aged and sick. The presence of such cross-resistance changes the treatment possibilities and tolerance factors such as previous antibiotic history of ciprofloxacin and having a history of an ESBL infection raises the chances of resistant strains. There is also an increase in hospitalization rates as the rates of antibiotic opposition increase to include ESBL complications. These results call for the prudent use of antibiotics and factoring resistance into the treatment of UTI illnesses.

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