HIGH RESISTANCE OF CIPROFLOXACIN AGAINST ESCHERICHIA COLI IN COMPLICATED URINARY TRACT INFECTION

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ABSTRACT

Objectives: To determine the risk factors for high resistance of ciprofloxacin against E. Coli in complicated urinary tract infections.

Material and Methods: It is an analytical study that was conducted in department of Urology (Team 'C') at Institute of Kidney Diseases Hayatabad Peshawar from 1st June 2012 till 31st December 2012. Total numbers of 100 patients with complicated UTI was selected in the study. Multivariate analysis and linear regression was performed for the detection of risk factors. All the data was recorded on structured Proforma and was analyzed on SPSS version 17.

Results: The mean age of the patient was 55.6 years (Range 3-82 years). Sixty-two patients were male while 38 patients were female. 66 isolates of E-Coli were found sensitive to ciprofloxacin while 34 isolates were found Resistant for ciprofloxacin. Using multivariate analysis and linear regression, an increasing age above 50 (p=0.002) History of urinary catheterization especially for bladder outflow obstruction (p=0.001) and previous multiple use of ciprofloxacin (p=0.001) and poor brand of ciprofloxacin were found to be independent risk factors for high resistance of ciprofloxacin.

Conclusion: The risk factors for emerging resistance are increasing age, urinary catheterization and multiple use and poor brand of ciprofloxacin

Key Words: Urinary tract, Infection, Ciprofloxacin, Urethral catheterization , Antimicrobial resistance.

INTRODUCTION

Urinary tract Infection is the most common disease in Urology Clinics across the globe: and still it bears significant morbidity and even mortality[1]. It is seen most of the time in Diabetic patients, Neurological patients, patients having structural abnormality in the urinary tract, and post catheterization or Cystoscopy[4]. UTI affect most commonly women and about one half of them presents in the clinics at some stage of their life[2]. Most common pathogen causing UTI are Eschchrechia coli found in 75-90% of isolates followed by Klebsiella and staphylococci in 5-15%[4,5]. Complicated urinary tract infection is defined as symptomatic cystitis or pyelonephritis in men or women with functional or structural abnormalities of urinary tract[3].

There are different antimicrobial therapies available for the treatment of UTI, but unfortunately there has been no guideline for the management of UTI that answers the optimum duration of treatment, the appropriate antibiotics, and the use of antimicrobials in special cases like paediatric age group, pregnancy, lactation and patients with renal or hepatic impairment.

Trimethoprim-sulphamethoxazole, Ciprofloxacin,Cephalospoins, and Nitrofurantoin are most common antibiotics used in the treatment of UTI[1,3]. Although the perception of clinician in our country favors. The rationale of our study is based upon research question that what are the risk factors for growing increase in antimicrobial resistance for ciprofloxacin? As still quinolones are widely used, considered and claimed best in complicated UTI. Our aim was to identify those risk factors so as to suggest some protocols for saving our arsenal of quinolones against common microorganisms causing complicated UTI.

MATERIAL AND METHODS

It is a co-relational analytical study conducted in department of Urology at Institute of kidney Diseases Hayatabad, Peshawar from June 2012 to December 2012. Total number of 100 patients with recurrent UTI resistant to Ciprofloxacin were included in study by non-probability convenient sampling.

Complete histories including all the variables of co morbid, primary or associated illness were obtained in all the cases. Thorough physical examinations were carried out in all the patients. Reports of relevant laboratory and radiological studies were obtained in all the

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patients. Urine culture and sensitivity were performed in main laboratory of Hayatabad Medical Complex in standard protocol. In order to find out the risk factors, we included only the cases of complicated UTI that were resistant cases to ciprofloxacin. We excluded bacterial isolates others than E Coli.

For determination of sensitivity, standard antibiotic tablets (Evan) Kirby-Bauer antibiotic testing (K-B testing) or disc diffusion antibiotic testing will be used. Antibiotic impregnated wafers were used for bacterial susceptibility for specific antibiotic. The results were interpreted as per the NCCLS guide lines 7. Data was collected on structured proforma. Multivariate analysis was performed using SPSS version 17. Odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors were calculated.

RESULTS

Total 100 patients with complicated UTIs were enrolled and their urinary samples were analyzed. The relations of age and sensitivity is shown in Table 1. The median age of the 62(62%) men and 38(38%) women was 55.6 years (Range 3-82 years). All patients were having complicated urinary tract infection. 66 isolates of E-coli were found sensitive to ciprofloxacin while 34 isolates were found resistant for ciprofloxacin. Sensitivity of UTI with ciprofloxacin is shown in Table 2.

DISCUSSION

UTI is the most common illness across the globe; unfortunately there are no uniform guidelines for use of antibiotics for the management of UTI. Quinolones are widely prescribed antibiotics in management of complicated UTI[2]. Once thought to be the most sensitive antibiotic in early 90s, ciprofloxacin is now facing increasing trend in antimicrobial resistance worldwide due to multiple reasons[8,9].

Table1: Cross tabulation of Culture and Age (n=100)

	Age (years)		Total
	Less than 50	**More than 50**	
Sensitive	37	29	66
Resistant	06	28	34
Total	43	57	100

OR 1.6; CI 1.09-2.46; p=0.002

The invention of antibiotics in 1928 has been declared as third great leap of human being, 10 Nitrofurantoin was considered highly effective and safe antimicrobial therapy for UTI in 5th and 6th decade of 20th century, but its spectrum of activity is limited. Amoxicillin and Co amoxiclav were introduced in the 1970, especially for management of respiratory and urinary tract infections, but the over use of amoxicillin led to the development of resistance to this antimicrobial, prompting a gradual shift to trimethoprim/sulfamethoxazole (TMP/SMX) as the first line therapy for UTI. However, wide use of TMP/SMX also resulted in the progressive emergence of resistance in the management of UTI. Fluoroquinolones offer an attractive alternative to TMP/SMX, and American and European guidelines recommend their empirical use in areas where TMP/SMX resistance is 10% or higher. Since its introduction Quinolones especially ciprofloxacin is most preferred antibiotics by clinicians in complicated UTI[2,10]. UTI is the disease of both genders of all ages as our age range was from 3-82 years. Our finding in this study is also in accordance with literature. Ciprofloxacin as most preferred antibiotic in complicated UTI but there is alarming increase in resistance to ciprofloxacin in our country ranging from 25-40% of patients in different studies. In America the resistance to Ciprofloxacin is in <10% of isolates whereas in Switzerland 27% of patients suffering from UTI are resistant to ciprofloxacin[3]. According to ARESC study data There is significant rise in the resistance in the countries like Spain Italy etc.[6]

There are several studies that have concluded that increasing age is risk factor in high resistance for ciprofloxacin; our study has also supported this fact that increasing age above 50 years is significant risk for high resistance of ciprofloxacin[11,12,13]. More over we tried to unfold the un answered question that why increasing age is a risk factor, the probable explanation is increasing age especially in male is associated prostatic enlargement that presents in majority of third world country as urinary retention which need urethral catheterization and antibiotic cover[14]. Our study has proved that history of catheterization and previous use of ciprofloxacin are independent risk factors for high resistance of ciprofloxacin with p value of 0.001 and < 0.005 respectively. A study by Park KH et al published in 2014 have also concluded that indwelling urethral catheterization and previous use of ciprofloxacin within 3 months are risk factors for high resistance of quinolones[15]. Another recent study by Garraffo and collegues

Table 2: Cross tabulation of sensitivily with primary disease

	Diabetes Mellitus	Gentourinary Malignancy	Glomerulo-nephritis	Congenital Anomalies	Urolithia-sis	Bladder outlet obstruction	Total
Sensitive	1	8	7	3	24	23	66
Resistant	2	2	3	4	11	13	34
Total	3	10	9	7	35	36	100
P value	0.987	0.99	0.994	0.987	0.986	0.985	

Table 3: Cross tabulation of Culture n Urethral Catheterization

Culture	Catheterized	Non catheterized	Total
Sensitive	19	47	66
Resistance	15	09	34
Total	44	56	100

OR 1.7; Cl 1.3-2.9; p 0.001

Table 4: Cross tabulation of Culture and sensitivity and previous Use of Ciprofloxacin within 3 months

Culture	One time	Multiple time	Total
Sensitive	24	42	66
Resistant	06	28	34
Total	30	70	100

OR 1.91;Cl 1.9-2.9; p<0.005

Table 5: Cross tabulation of Culture n brand of Ciprofloxacin

Culture	National Pharma	Multi-national Pharma	Not remembered	Total
Sensitive	29	29	8	66
Resistant	20	10	4	34
Total	49	39	12	100

OR 1.8;Cl 1.3-2.9; p=0.002

on complicated UTI have also supported the argument that previous history of catheterization and use of antibiotics are risk factors for emerging resistance of quinolones[16].

Overuse and abuse of antibiotics in developing countries like Pakistan is major health issue with emergence of antimicrobial resistance to the common flora in different infections. The mushroom growths of national pharmaceutical industry manufacturing doubtful brands of quinolones have raised concerns in health regulatory authorities[17,18]. Unfortunately there are very few studies that had addressed this burning issue of public interest. A recent study by Raheel Bano et al has found the gross diversity among different brands of levofloxacin in terms of standardization, dissolution and in vitro efficacy in UTI[19]. The studies from India, Bangladesh and Nepal have also highlighted this general fact[20]. Our study have also shown that national brands of ciprofloxacin is significant risk factor in emerging resistance in complicated UTI.

Although there is consensus among most of the authors that presence of diabetes mellitus does not possess a risk in higher resistance for quinolones; same was found in our study but controversy still prevails about nature of primary disease like urolithiasis, uro-oncolgy and congenital anomalies as risk factors for high resistance of quinolones in complicated UTI. Some authors have cited that obstructive Uropathy, urolithiasis and even gynecological surgeries are potential risk factors in high occurrence of resistance[11]. However present study could not prove significant relation between primary disease and high resistance for ciprofloxacin. A benchmark study by Hande Arslan has also concluded in our favor that nature of primary illness is not a risk factor in emerging antimicrobial resistance[21].

Our study is implicated on urologists, general surgeons, medical specialist and even family physicians who are involved in management of UTI. More over our study is also an alarm bell to health regulatory authority in federal and provincial capitals to take considerable action in implementing standard manufacturing protocols for national pharmaceutical industry. Our study has come up with a big question mark of an unanswered question that what has gone wrong in the manufacturing of national pharmaceutical industry that is adversely affecting the society in form of increasing resistance for ciprofloxacin against E Coli in complicated UTI. So further study is desired on this unanswered question.

CONCLUSION

Increasing age above 50 years, History of urethral catheterization, previous use of ciprofloxacin within 3 months duration and poor brand of ciprofloxacin are independent risk factors in high resistance for ciprofloxacin in complicated UTI.

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