Original Article

"ANTIBIOTIC RESISTANCE OF FLUOROQUINOLONES AMONG THE GRAM NEGATIVE BACTERIAL UROPATHOGENS AT A TERITIARY CARE CENTRE"

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Abstract: Fluoroquinolones resistance in urinary tract pathogens has been increasing globally due to use of urinary catheters and poor health sevices. we studied the the quinolone resistance pattern in gram negative bacterial uropathogens at a teritiary care centre in Kanpur. **Materials and methods**: In this prospective study 990 sample were studied. Urine samples were collected and processed by using standard microbiological procedures in Rama medical college hospital &research center, Kanpur. **Result:** Among 990 urine samples, 297 (30%) were positive cases of urinary tract infection, among these 110 (11.1%) were resistant to fluoroquinolones. UTIs were mostly seen in 30-49 year females and 40-49 year males. E.coli (67.0%) was the most common isolate. 82.4% of E.coli, 60.6% of K.pneumonia, 81.1% of K.oxytoca, 81.8% of Proteus were resistant to all the quinolones antibiotics. All the isolated uropathogens were highly resistant aminoglycosides and carbapenem also but gave better sensitivity against nitrofurantoin. **Conclusion:** Because of higher resistance fluoroquinolones may no longer be effective as first line therapy for gram negative UTI in hospitalized patients. Nitrofurantoin can be a alternatives of the drug of choice in most clinical settings.

INTRODUCTION

Urinary tract infection (UTI) is the colonization of microorganisms in urinary tract, predominantly caused by bacteria [1]. There is an estimated 150 million urinary tract infections per annum worldwide [2]. Complicated and hospital acquired UTIs are caused by both gram negative as well as gram positive bacterial species.[3,4] It is important to know the clinical history of the patients as well as the microbial resistance pattern of a community before prescribing the antibiotics. Resistance to amoxicillin, trimethoprim-sulfamethoxazole has led to increased use of fluoroquinolones. Fluoroquinolone resistance in UTI pathogens has been increasing globally, may be due to recent hospitalization, urinary catherization and poor health.[3] Quinolones are a family of broad-spectrum antibiotics that kill bacteria by inhibiting DNA replication. Mutations in the chromosomal genes that lead to alterations in the drug

targets, overexpression of efflux pumps plasmids carrying resistant genes, are found to be the major reasons for developing resistance. Norfloxacin, Ciprofloxacin and Levofloxacin are the most commonly used quinolones.[3] This resistance pattern may differ between geographical areas, gender and age. This study was undertaken to know the quinolone resistance pattern in gram negative bacterial uropathogens at a teritiary care centre in Kanpur.

MATERIALS AND METHODS

This prospective study which was conducted in the Department of Microbiology in Rama Medical College Hospital and Research Centre, over a period of 4 months, starting from 1st November 2015 to 31 march 2016. A total number of 990 sample were included in this study. Clearance from the institutional ethical committee was obtained. Informed consents were taken from all the patients. Urine samples were collected by standard mid-stream "clean catch" method from all the patients, in sterile, wide mouthed containers that were covered with tight-fitting lids. The samples were processed by using standard microbiological procedures. The specimens were cultured on dried plates of Cystine Lactose Electrolyte Deficient agar, by standard loop method and the plates were incubated at 37°C overnight. Culture results were interpreted as per CLSI guidelines 2016 [5] antibiotic susceptibility was done for all culture positive isolates by Kirby Bauer disc diffusion method on Mueller –Hinton agar (Himedia, Mumbai).

RESULTS

A total of 990 urine samples, 297 (30%) were positive cases of urinary tract infection, among these 110 (11.1%) were resistant to fluoroquinolons. Age and sex distribution was shown in **Table-1**. E.coli (67.0%) was the most common isolate followed by Klebsiella pneumonia (11.1%), K.oxytoca (7.41%), Enterobacter aerogens (5.38%), Citrobacter fruendii (3.70%), Proteus mirabilis (3.70%), and Citrobacter koseri (1.68%). Fluoroquinolons resistant pattern of isolates were shown in **Table-2**. 82.4% of E.coli, 60.6% of K.pneumonia, 81.1% of K.oxytoca, 81.8% of Proteus were resistant to all the quinolones antibiotics. [**Fig 1**] Antimicrobial resistance pattern of quinolones resistant isolates has shown in **Fig. 2**.

DISCUSSION

Fluoroquinolone resistance (FQR) is increasing in UTI gram negative pathogens both locally and regionally.

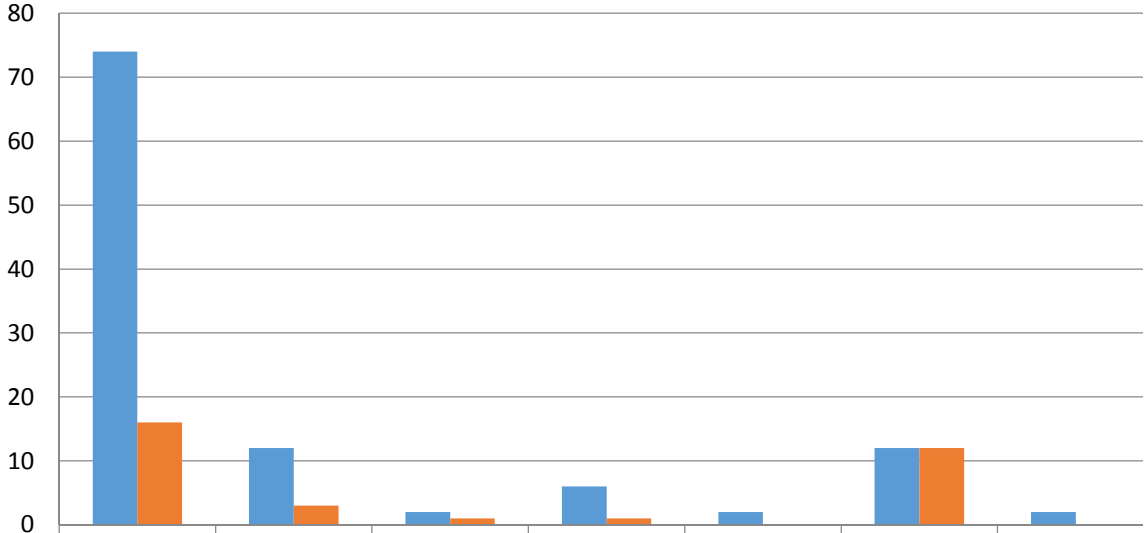
Table 1: Age and Gender wise distribution among gram negative Uropathogens

		E.coli	K. pneumoniae	K.oxytoca	Enterobacter aerogens	Citrobacter frundi	Proteus mirabilis	Citrobacter koseri
Male	<20	2	1	-	-	-	-	-
	21-29	4	1	1	1	1		-
	30-39	16	2	1	1	1	1	-
	40-49	20	3	1	1	1	1	-
	50-59	14	4	2	2	1	1	1
	>60	5	2	1	2	1	2	1
Female	<20	4	1	1	-	-	-	-
	21-29	23	1	2	1	1	-	-
	30-39	47	5	5	1	1	1	1
	40-49	33	4	3	2	1	1	1
	50-59	20	4	2	2	1	2	-
	>60	11	5	3	3	2	2	1
		199(67%)	33 (11.1%)	22 (7.41%)	16 (5.38%)	11 (3.70%)	11 (3.70%)	5 (1.68%)

Table -2 :Fluoroquinolons resistance pattern of Gram negative bacilli

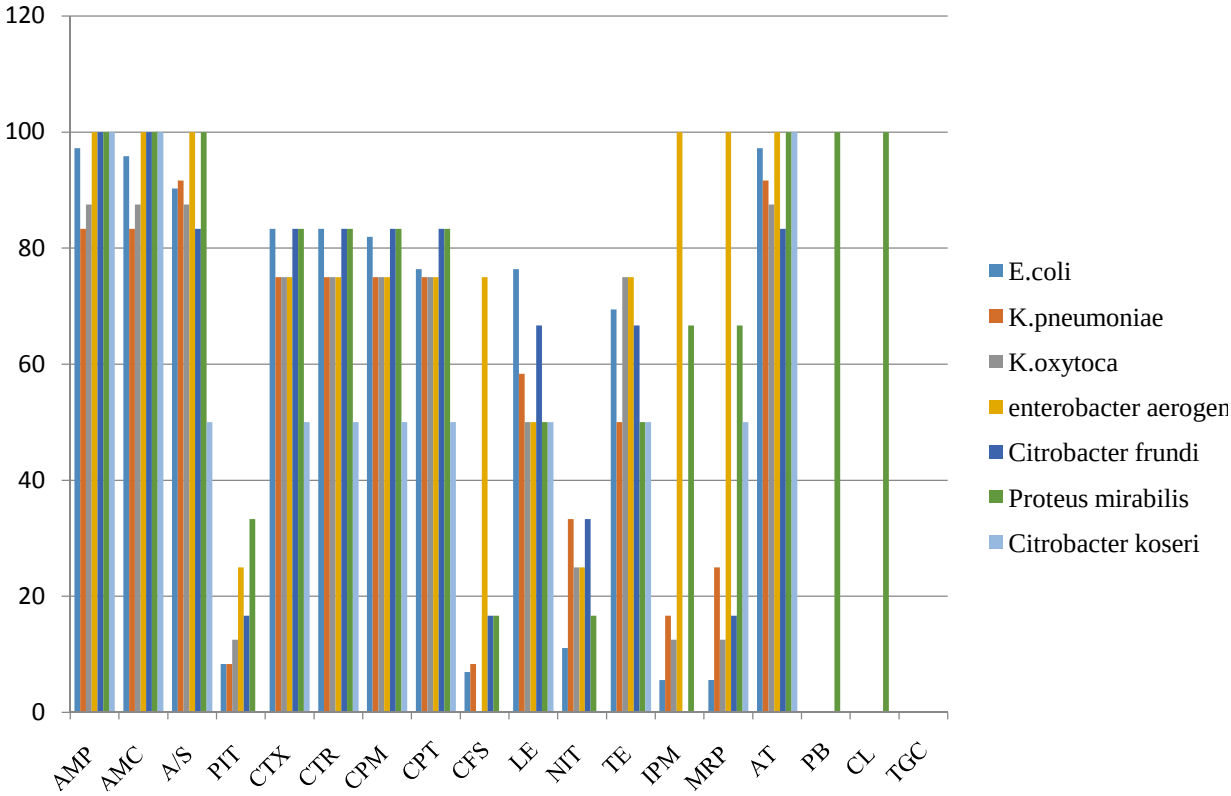
	CIP	**LE**	**NX**
E.coli	**83.92**	**82.41**	**90.45**
K.pneumoniae	**60.61**	**75.76**	**90.91**
K.oxytoca	**90.91**	**81.82**	**90.91**
Enterobacter	**81.25**	**75.00**	**81.25**
Citrobacter fruendi	**81.82**	**72.73**	**100.00**
Proteus mirabilis	**81.82**	**81.82**	**90.91**
Citrobacter koseri	**80.00**	**80.00**	**80.00**

Fig 1 : Distribution of Fluoroquinolons Resistant Uropathogens



	E.coli	K.pneumoniae	K.oxytoca	Citrobacter frundi	Enterobacter	Enterococci	MSSA
Isolates	74	12	2	6	2	12	2
resistant	16	3	1	1	0	12	0

Fig– 2: Antibiotic resistance pattern of Fluoroquinolones Resistant Organisims



Close monitoring of resistance patterns may prove useful in directing empiral treatment both in uncomplicated and complicated cases. This study highlights the resistance pattern of the isolates to fluoroquinolones, however, the absolute proportion of resistant strains must be interpreted with caution, because routine bacteriological testing is usually selectively done for cases following failure of empirical treatment.

Fluoroquinolone resistance varied from country to country and less so, but significantly nevertheless, from region to region. The highest regional FQR rate was seen in Latin America at 38.7%, but resistance was as high as 70% in one hospital in Panama and above 40% from three sites in Puerto Rico and Mexico.[6] The average for the Asian countries was 33.2%. Fluoroquinolone resistance rates for Canada and the United States were 22% and 24%, respectively, and were more than double the rate reported as recently as 2006 by Karlowsky et al., in 1,858 E. coli [7]. Notably, the current rate of 49% resistance seen in Turkey is also almost double the 25% rate reported for that region during the same 2005-2006 time frame but that report was limited to E. coli only [8]. The lowest rates reported in this study were also seen in India, Estonia and the United Kingdom, however, the significance of this is diminished due to the low n's and the fact that the isolates were collected from a single lab in each country.

Many studies have shown majority of females had acquired UTIs, has an higher rate compared to male as in our study.[3,9,10,11]

Asrat AA et.al.[3] reported 54.71% from female patients of 16-35 years had UTIs and in our study 30-49 year female and 40-49 year male suffered from UTIs This supports the idea women UTIs were more common among women of reproductive age groups which agrees with earlier studies in this country [12] identified sexually active and/or probably pregnant females in this age group are at high risk for UTI.

In the present study E.coli (67%) was the most predominant isolate followed by Klebsiella pneumonia (11.1%). Many studies also found E.coli as a predominant uropathogen. Asrat AA et.al., Niranjan et.al. and in our previous study 60%, 76.51% and 45.61% of E.coli was reported. [3,13,14] The in vitro activity of the drugs in this study suggests that there are relatively few therapy alternatives for treatment of fluoroquinolones-resistant gram-negative

UTI pathogens. Low susceptibility rates were seen for ampicillin-sulbactam, cefotaxime, cefoxitin, ceftazidime, and ceftriaxone against the majority of isolates. Only ertapenem and imipenem demonstrated consistent activity against ESBL+ isolates, with both equally active against ESBL+ E. coli, imipenem more active against ESBL+ K. oxytoca, and ertapenem more active against ESBL+ P. mirabilis. None of the study drugs were more than 88% active (imipenem) against all K. pneumoniae. Overall, amikacin and piperacillin-tazobactam had similar in vitro activity to ertapenem and imipenem against all FQR isolates combined. [6] Nitrofurantoin is bactericidal in urine at therapeutic doses, and its multiple mechanisms of action appear to have enabled it to retain potent activity against *E. coli* despite nearly 50 years of use [15]. The consistent and high-level susceptibility of *E. coli* to nitrofurantoin may be influenced by nitrofurantoin's narrow spectrum of activity, limited indication (treatment of acute cystitis), narrow tissue distribution (low or undetectable serum concentrations), and limited contact with bacteria outside the urinary tract [16].

A distinction was made in the collection time of the UTI specimen to categorize the infection as HA (specimen collection ≥48 after admission) or CA (specimen collection 0.05). This may reflect the growing numbers of community-acquired ESBLs containing the CTX-M-15 ESBL genotype that is strongly associated with multi-drug resistant phenotypes including fluoroquinolone resistanc.

Limitations of this study: Lack of molecular characterization of resistance mechanisms.

CONCLUSION

These observations suggest that fluoroquinolones may no longer be effective as first line therapy for gram negative UTI in hospitalized patients. And still nitrofurantoin remains the drug of choice in most hospital settings.

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