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FUOROQUINOLONES RESISTANT ESCHERICHIA COLI A UROPATHOGEN NEEDS-URGENT MONITORING AND SURVEILLANCE: A PILOT STUDY BETWEEN 2014 TO 2016.

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ABSTRACT

Urinary tract infection (UTI) second largest disease, with developing antibiotic resistant strains in uropathogens, pulls attention and concern in medical treatment over the past years. The most common uropathogens found is *Escherichia coli* (*E. coli*), commonly treated by fluroquinolones for UTI infections.[1] **Aim:** Our study aimed at evaluating the antimicrobial patterns of common uropathogen Escherichia coli towards the frequently prescribed fluroquinolones for uncomplicated UTI in our tertiary care hospital at Mangadu South India, during Aug 2014 and July 2016. **Study Subjects & Results:** A total of 4217 urine samples analysed, common uropathogen was identified as E.Coli. (53%) from uncomplicated UTI patients. Antimicrobial susceptibility performed for *E. Coli* towards the five common fluroquinolones, shows susceptibility as 62.4 % Gatifloxacin, 73.6% Levofloxacin 70.4% Ofloxacin 55.6% Norfloxacin, and only 39 % Ciproflox, were effective for treatment of UTI. High resistance was noticed towards Ciprofloxacin, Norfloxacin and the overall resistance toward the commonly used fuoroquinolones is between 25-30% which needs early attention. **Conclusion:** Study was able to analyse the fluroquinolone pattern of antibiotic treatment within the uncomplicated UTI patients group in our hospital.

KEYWORDS: Urinary tract infection, Fluroquinolones, Gram negative bacteria, Antimicrobial resistance.

INTRODUCTION

The urinary tract infections (UTI) is the second commonest infections, commonly caused by the single uropathogen the Escherichia coli, and frequently isolated from different clinical specimens of diarrhoea.[2] *E.Coli* gains clinical importance due to its cosmopolitan nature, ability to initiate, establish and cause various kinds of infections. Resistance among the enterobacteriaceae relates to the increasing usage of antimicrobial agents, irrational use of antibiotic, incomplete course of therapy, self-medication and impared immunity. Previously fuoroquinolones resistance in uropathogens was very rare. Current literature shows greater resistance in *E.Coli* has emerged, and continues to increase exceeding 50% in some parts of the world, particularly in Asia and developing countries by surveillance studies.[3] One to two-thirds of Enterobacteriaceae producing extended spectrum β-lactamases were fluoroquinolone resistant too. Due to the increasing resistance seen in Escherichia coli, the management of urinary tract infections is becoming complicated with limited therapeutic options,[2] Fuoroquinolones seems to be used extensively in the management of genitourinary infections especially acute uncomplicated cystitis. There is a need for a constant surveillance of resistance rates among Escherichia coli isolates to ensure appropriate recommendations for fluroqunolones in treatment of urinary tract infections. Based on these data our study is designed to analyse the pattern of E.coli to the common fluroquinolones used in our population at Chennai South India.

AIM AND OBJECTIVE

Our Study aimed at gaining knowledge about antimicrobial patterns of common uropathogen *Escherichia coli*, towards the frequently used fluroquinolone in our tertiary care hospital at Mangadu South India, between Aug 2014 and July 2016. The frequently used fluoroquinolone drugs analysed in our study, were Norfloxacin, Ciprofloxacin, Ofloxacin, Levofloxacin and Gatifloxacin.

MATERIALS AND METHODS

A prospective analysis was done at the department of microbiology. The study subjects were patients attending the outpatients and inpatient units of Sri Muthukumaran

Medical College Hospital and Research Institute near Mangadu, South of Chennai. A total of 4217 clean catch single, mid-stream, urine specimen was collected from patients during August 2014- April 2016. Clinical Details was noted, urine culture was done and analysed in the department of Microbiology.

Methods of Isolation and identification

A measured amount of urine, using calibrated loop method was inoculated onto Nutrient, Blood and MacConkey agar plates by streaking method. Inoculated plates were incubated aerobically at 37°C for 24 hours. Identification of pure isolates was done by observing morphological, cultural and biochemical characters. "A culture with growth of potentially pathogenic bacteria was normally considered positive if the number of colony forming units per liter (CFU/mL) was10^5. Reference strains from the American Type Culture Collection (ATCC) 25922 E.coli were used for control of the susceptibility determinations. Antibiotic sensitivity testing was performed using the Kirby–Bauer disc diffusion method according to the Clinical and Laboratory Standards Institute Guidelines**.** Dermographic data on the type of bacterial isolates from the urine specimens and antibiotic susceptibility patterns for the five fluoroquinolones were tested against *E.Coli* culture positives for the study purpose. Antimicrobial drug susceptibility testing for Norfloxacin (10 µg), Ciprofloxacin (5 µg), Levofloxacin (5 µg) and Gatifloxacin (5 µg) and was done on all *E.Coli* isolates. Interpretation of results was done based on the diameter of the zone.

RESULTS

Figure I shows the Age group and Sex analysis among the study subjects. Our study showed maximum growth among 41 to 60 years, a higher percentage in Females than males.

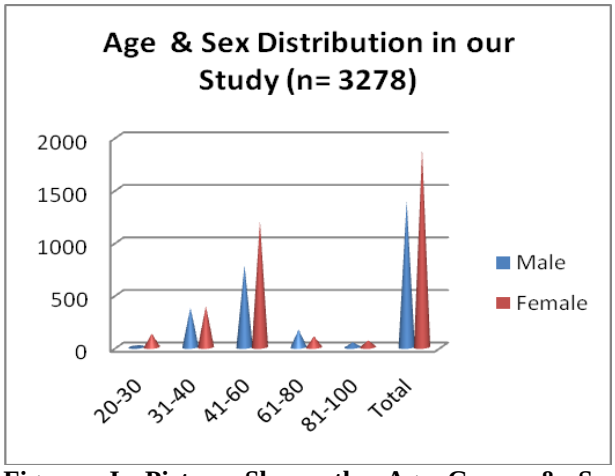

Figure –I: Picture Shows the Age Group & Sex Distribution among the Uropathogen positive subjects.

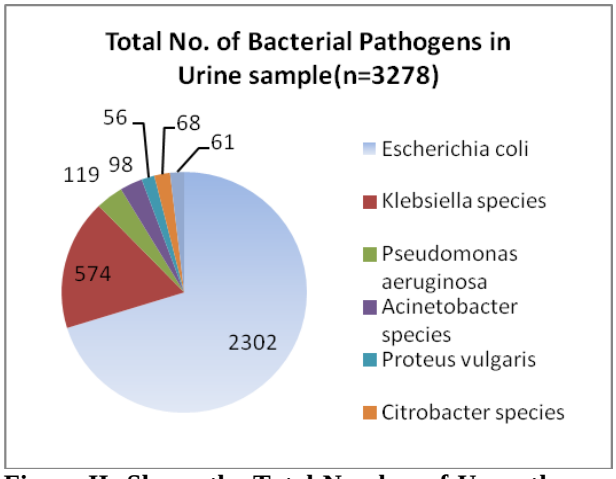

Figure II: Shows the Total Number of Uropathogens in our study group.

Among 4217 samples analysed 778 had no growth, 161 had mixed growth, non pathogenic contaminant, and uropathogens were seen only in 3278 only. Further, analysis among 3278 uropathogen showed *E.Coli* (2302) 70.1%, major cause of UTI infections. The breakup of uropathogens in our study shows the following results in Fig II. Among the 3278 the major uropathogen, 2302 (70.2%) E.Coli, followed by 574 (17.5%) had Klebsiella sps other gram negative pathogens isolated from urine samples are Acinetobacter species 98(2.9%), Pseudomonas species 119(3.6 %), Proteus species 56 (1.7%), Citrobacter species 68 (2%) and Enterobacter species 61 (1.8%).

Table I- Shows the Overall susceptibility pattern of fluroquinolones to *E.Coli.*

Overall Resistance & Susceptibility pattern of each fluoroquinolones to Escherishia coli n=2302				
Drugs	**Susceptible**		**Resistance**	
	Total (n)	Percentage (%)	Total (n)	Percentage (%)
Norfloxacin	1279	55.6	1023	44.4
Ciprofloxacin	897	39	1405	61
Ofloxacin	1621	70.4	681	29.5
Levofloxacin	1696	73.6	606	26.3
Gatifloxacin	1438	62.4	864	37.5

Our study reveals only the culture positive *E.Coli* total number of 2302 towards the antibiotic susceptibility for frequently used Fuoroquinolones i.e Ofloxacin, Norfloxacin, Ciprofloxacin, Levofloxacin, and Gatifloxacin, since, the present study was undertaken to detect the current antibiogram pattern of Escherichia coli with a special reference to common fuoroquinolones used in our hospital and local population.

Escherichia coli showed the following resistance: Norfloxacin (44.4%), Ciprofloxacin (61%), Levofloxacin (26.3%) is followed by Ofloxacin (29.5%), and Gatifloxacin (37.5%). Our study showed high resistance to ciprofloxacin and Norfoxacin and all other

fluroquinolones used were showing 25% of resistance that needs attention in future antibiotic policy evaluation.

DISCUSSION

Global surveillance studies demonstrated that fluoroquinolone resistance has increased in the past among all bacterial species.[4] Urinary tract infections are often treated empirically; susceptibility tests are often carried out only when the patient has failed one or more courses of antibiotics. Antimicrobial therapy for treatment of UTIs especially when using the quinolones should be based on local experience of sensitivity, tolerability and resistance patterns.[5] While fluoroquinolone resistance in uropathogens was once rare, resistance in *E. coli* has emerged and continues to increase. Fluoroquinolone resistance occurs through multiple mechanisms including chromosomal point mutations in the genes encoding DNA gyrase and/or topoisomerase iv, mutations that cause decreased expression of outer membrane proteins (OMPs), alterations in the lipopolysaccharide (LPS) component of the cell envelope, and enhanced fluoroquinolone effl ux by effl ux pumps such as AcrAB (Chenia et al 2006; Chang et al 2007). Plasmid-borne resistance has also recently been discovered, and is caused by protection of DNA gyrase and topoisomerase IV by Qnr-like proteins, including QnrA (Chenia et al 2006). Antibiotics sometimes cause problems instead of life saving weapons against microorganisms. Surveillance of urinary isolates collected between 1989 and 1997 found that fluoroquinolone resistance in *E. coli* was essentially nonexistent during this time frame.[6] More recently, results of the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study, a multicenter surveillance study performed between 2003 and 2004 in the US and Canada, reported that overall resistance rates to ciprofloxacin and levofloxacin were 5.5% and 5.1%, respectively.[7]

Currently, fluroquinolones forms the preferred group of drugs for UTI due to strong antibacterial effects and ease of administering both orally and parenterally. However, there is a developing resistance to quinolones as is the case with other antibiotics. Our study is the first of its kind to know the fluroqunolone susceptibility in our region. Our study shows *E. coli* was the commonest pathogen causing in uncomplicated UTI, that correlates well with others.[8] Our study, reveals the importance for monitoring the common fluroquinolone used in our community to have strong resistance among the commonest UTI organism the *E.coli.* Further, the pattern of Resistance to Ciprofloxacin (61%) followed *by Norfloxacin* (44.4%), *Gatifloxacin* (37.5%), *Ofloxacin* (29.5%) and *Levofloxacin* (26.3%) was correlating with previous authors by Gupta et.al.[9] proving 70 % resistance to norfloxacin, 60 % resistance to ciprofloxacin and 59 % resistance to levofloxacin. y Ullah et.al showed resistance rate of Escherichia coli to ciprofloxacin (68.9 %) ofloxacin (40.4%). (62.1 %) resistance to ciprofloxacin, (58.6 %) Levofloxacin and ofloxacin (28.6%) was shown by Hyuk et al. Our study also correlated with high resistance developed in Ciprofloxacin than with other fluroquinolones as supported by various authors. Though only the commonly used five major fluroquinolones were studied we observed that there were some 358 (18.3%) of resistance seen among the single *E.Coli* uropathogen to all drugs. Antibiotic susceptibility of microbial agents depends upon the region where the agent was isolated .The emergence of resistance for fluoroquinolones is multifactorial. Further, Genes determining resistance to fluoroquinolones are located in the bacterial chromosome. Point mutations in gyrA and gyrB genes cause loss of the main target locus for fluoroquinolones. Resistance is low grade, develops when the concentration of the chemotherapeutic in the kidneys or urine is close to the MIC (minimal inhibitory concentration)**.** Another research shows additional mutations, also in acr R and ma rR genes produce a higher grade of resistance to fluoroquinolones, by an RND-type (resistance- nodulation-division family) pump, i.e. AcrAB-TolC, which is found in Escherichia coli These mutations occur with a significantly lower incidence. The resistance of Gram-negative rods is also influenced by the availability of OMP (outer membrane protein) channels, through which the chemotherapeutic enters the cell. Tran and Jacoby in 2002 discovered the qnr gene, which protects gyrase against the cidal effect of fluoroquinolones**.** Usually the treatment of urinary tract infection (UTI) has to be answered by comparing their antimicrobial activity against uropathogens, the pharmacokinetic and pharmacodynamic parameters and outcome of statistically meaningful clinical studies. Anti microbial activity of the commonly used fluroquinolone agents have not been studied in our hospital, whether all fluoroquinolones give equivalent results with short term therapy of acute uncomplicated UTI is a query. The study reveals antimicrobial resistance has emerged against fluoro-quinolones possibly due to irrational use of antibiotic, incomplete course of therapy and the self-medication. Although our study reveals the importance of resistance developed among the commonly used fluroquinolones in-vitro susceptibility may vary with in-vivo against different clinical isolates. There is a need to rationalize the use of fluoroquinolones in order to prevent the dissemination of resistant strains in the population.[10]

SUMMARY & CONCLUSION

The growing problem of fluroquinolone resistance associated with multidrug antimicrobial resistance becomes a major concern in many countries. Our study co-relates with many authors in the prevalence of E.Coli that are responsible for urinary tract infections, along with invitro resistance to fluroquinolones. Common uropathognes analysed also gives a similar report from other hospitals and regions that are associated with multidrug-resistant phenotypes. Our data will surely help in determining the antimicrobial susceptibilities to fluroquinolone in our local population. These data may

be used to determine trends in antimicrobial susceptibilities, to formulate local antibiotic policies, to compare local with national data and, overall, to assist clinicians in the rational choice of antibiotic therapy and to prevent misuse, or overuse, of antibiotics. The random uses of the drugs should be avoided, antimicrobial susceptibility test results should be considered when planning the therapy. Our study shows the need to closely monitor the development of fluroquinolone resistance. Further, such studies will help in drug development. Paucity of new antimicrobial drugs for common infections like UTI which may continue to worsen in future.

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