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Pattern of Antimicrobial Resistance of *Escherichia coli* Isolates from Urinary Tract Infection Patients: A Three Year Retrospective Study

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ABSTRACT

Objectives: To study the changing pattern of antimicrobial resistance of *Escherichia coli* isolates from patients of urinary tract infections over last three years
Materials and Methods: A retrospective, record based study carried out based on the records of Culture and sensitivity (C/S) reports of indoor patients, during past three years (2012 - 2014). The type of organisms most common in urine sample was noted and the drugs still effective for the particular organism were noted.
Results: *E. coli* was the most frequent isolate throughout the three years (67.66 % of the total isolates). Analysis of the results year wise indicated that the lowest percentage of resistance was manifested against imipenem between 11.86 % (2012) and 11.36 % (2014). Resistance for nitrofurantoin decreased over the three consecutive years from 36.1 % (2012) to 18.15 % (2014). Over the successive years, resistance to ceftriaxone tends to increase from 53.39 % (2012) to 73.33 % (2014). E coli showed absolute resistance (100 %) to cotrimoxazole and tetracycline. On an average over the three years *E. coli* showed high amount of resistance to fluoroquinolones (75 %) and aminoglycosides (67 %).While Multi drug resistant (MDR) *E. coli* range between 63 % (2012) to 65 % (2014).
Conclusion: The antimicrobial resistance patterns are constantly evolving and vary from region to region it has become a necessity to do constant antimicrobial sensitivity surveillance. This will help clinicians to provide safe and effective empirical therapies.

INTRODUCTION

Urinary tract infections (UTIs) are one of the commonly encountered diseases in developing Countries with an estimated annual global incidence of at least 250 million (Ronald *et al.*, 2001). Antibiotic resistance is a worldwide problem threatening our ability to treat infections (Fagan *et al.*, 2015).Treatment failure because of antibiotic resistance inside and outside hospitals results in increasing mortality, morbidity and economic costs. In most instances, growth of more than 105 organisms per millilitre from a properly collected midstream "clean-catch" urine sample indicates infection (Sundqvist *et al.*, 2009). *Escherichia coli* (*E. coli*) is the major aetiological agent in causing UTI, which accounts for up to 90% of cases with other pathogens including *Enterococci*, *Staphylococcus saprophyticus*, *Klebsiella* spp., Proteus mirabilis and *Pseudomonas* (Ronald, 2002). In addition to Urinary Tract, *E. coli* is the most frequent pathogen associated with Intra-Abdominal Infection (IAI) (Jafri *et al.*, 2014). In UTI cases, antibiotic treatment is often started empirically, before the results of urine culture are available and therapy is based on information obtained from the antimicrobial resistance pattern of the urinary pathogens (Ashkenazi *et al.*, 1991). Regular monitoring of resistance patterns is necessary to improve guidelines for empirical antibiotic therapy (Grude *et al.*, 2001). Empirical first-line treatment of uncomplicated UTI should preferably be with an antibiotic to which resistance is low and which has a low capacity for co-selection of resistance and a low impact on the normal intestinal flora (Kahlmeter, 2003; Naber, 2008).

Resistance pattern of microorganisms vary from country to country, state to state, large hospital to small hospital and hospital to community. The estimation of local aetiology and susceptibility profile could support the most effective empirical treatment (Farajnia *et al.*, 2009).

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In our country, the problem of antibiotic resistance is compounding because of overuse and misuse of antibiotics. There is no systematic national surveillance of antibiotic resistance and insufficient data is available to quantify the problem. The aim of this study was to evaluate the in vitro resistance pattern to commonly used antimicrobial agents. This study will further help in formulating most optimal empirical treatment regimen for UTI cases, while awaiting Culture and sensitivity reports with minimal therapeutic failure. It also reflects changes in the susceptibility pattern of the most common uropathogen *E. coli* over the years in this area, implying the need for periodic monitoring in order to decrease the number of therapeutic failures and to add on the effort to contain the increasing antibiotic resistance.

MATERIAL AND METHODS

A retrospective, record based study was carried out in department of Pharmacology in collaboration with Microbiology department of a teaching tertiary care hospital. The study was carried out based on the records of C/S (Culture and sensitivity) reports of indoor patients, during past three years from January to December of years 2012 to 2014 admitted in wards of Rajindra Hospital and Govt. Medical College Patiala, a tertiary care 1100 bedded hospital. Permission was taken from ethical committee and in-charge of Microbiology laboratory prior to the study. All the C/S reports of urine samples, maintained in the record registers of Microbiology laboratory received from various wards during the period 2012 to 2014 were included and analyzed. Reports of Isolates from repeat culture of previously recruited patients and isolates identified as commensals or contaminants were excluded from the study. No. of reports /yr for three years of urine samples which were already registered were noted. Only reports with positive *E. coli* c/s report were considered for this study. Positive reports for *E. coli* out of total no. of urine samples positive for the years 2012, 2013 and 2014 were 590 (947), 707(1058) and 810 (1102) respectively. Sample size for the present study was 2, 107 for the three years.

The data was collected year wise starting from the year 2012.The provisional diagnosis was noted. Antibiotic sensitivity pattern of *E. coli* isolates was determined on Muller Hinton agar plates by Kirby-Bauer disc diffusion method. Isolates were declared as sensitive or resistant on the basis of zone of inhibition following the criteria of Clinical Laboratory standards Institute (CLSI) (Niranjan *et al.*, 2014). The surface of Mueller Hinton agar plates was streaked by a sterile cotton swab. The Mueller Hinton agar plates were allowed to dry before applying antibiotic disc. Then, Filter paper disks impregnated with fixed amount of antimicrobial drugs were gently and firmly placed on the agar plates, which were then left at room temperature for 1 hour to allow diffusion of the antibiotics into the agar medium. The plates were then incubated at 37°C for 24 hours. An inhibition zone formed around the disc showed an antimicrobial activity present on the plates. The diameter of the inhibition zones was measured in millimeter at 24 hours using a scale. The antibiotics tested were broad-spectrum Penicillin, third generation Cephalosporin, Quinolones, Tetracycline, Aminoglycosides, and Sulfonamides, Carbapenems and Nitrofurantoin. Type of organisms most common in urine sample were noted and drugs still effective for the particular organism were noted.

Whole of the data was collected and compiled in the year wise manner and compared year wise to see the trend in the resistance pattern. An isolate was considered as MDR if found resistant to three or more antimicrobials belonging to different classes/groups of antimicrobials (Niranjan *et al.*, 2014). C/S reports for other common uropathogens will also be further analyzed.

Statistical analysis: Descriptive statistics was used for analysis. Proportions were used to study the resistance pattern of *E. coli* and variables were expressed as percentages. Licensed SPSS version 20 was used for statistical analysis. All the data was expressed as tables and bar diagrams.

RESULTS

Over a 3-year period of 2012-2014, a total of 2, 464 positive urine isolates including 2, 107 *E. coli* were analyzed. As expected, *E. coli* was the most frequent isolate throughout the three years (average of 67.66% of the total isolates). The next most frequently isolated bacteria were *Klebsiella pneumonia* (14%), Proteus sp. (6%), *Pseudomonas aeruginosa* (8%), *Enterococcus* sp. (2%), and *Streptococcus agalactiae* (1%). Analysis of the results year wise indicated that the lowest percentage of resistance was manifested against imipenem between 11.86%, 12.22% and 11.36% for the years 2012-2014 [Table1]. Resistance for nitrofurantoin decreased over the three consective years from 36.1% (2012) to 18.15 % (2014). Over the successive years, the resistance to third generation cephalosporins, tends to increase on an average from 50% to 65%. *E coli* showed absolute resistance (100%) to cotrimoxazole and tetracycline. Two most common classes of drugs used for treatment of Urinary tract infections are fluoroquinolones and aminoglycosides. *E. coli* showed high amount of resistance of 75% and 67% respectively for the two groups over the three years along with the increasing trend [Figure1].

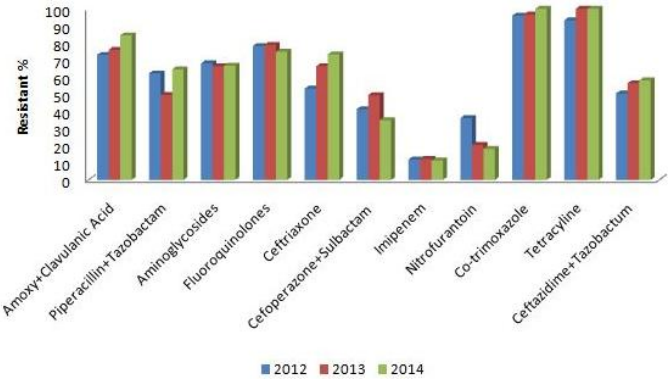

Fig. 1: Antibiotic resistance pattern of *E. coli* isolates in UTI patients over last three years from 2013 to 2014.

MDR (Multi -Drug resistant) *E. coli*

Those strains which are found to be resistant to three or more than three groups of antimicrobials were taken as multi drug resistant strains. While MDR *E. coli* percentage resistant to fluoroquinolones, third generation cephalosporins and aminoglycosides range between 63 % (2012) and 65 % (2014) over the consecutive years.

DISCUSSION

This study shows the distribution of microbial species and antibiotic resistance patterns of *E. coli* isolated from North Indian patients with UTI. Rajindra hospital is an 1100-bedded hospital located in Patiala, Punjab; it is one of the busiest hospitals in the state. Antibiotic resistance is a major clinical problem in treating infections caused by these microorganisms. The resistance to the antimicrobials has increased over the years. Resistance rates vary from one region to another (Farrell *et al.*, 2003; Mathai *et al*., 2001). There are very few studies done in Punjab for keeping a check on the changing trend in antimicrobial resistance.

Gram‐negative organisms are the most common organisms causing UTIs. In this study, *E. coli* accounted for approximately 68% of all clinically significant urinary isolates followed by Klebsiella (14%), Proteus sp.(6%), *Pseudomonas aeruginosa* (8%), *Enterococcus* sp.(2%), and Streptococcus agalactiae(1%). The spectrum of uropathogens isolated from urine samples in this study is very similar to the studies done in different regions of India (Prakash *et al.,* 2013; Mukherjee *et al.,* 2013; Akram *et al.,* 2007). In our study, *E. coli* isolates found to be resistant to Amoxicillin-clavulanate between 73% (2012) and 84%(2014).Such high level of resistance of 70% and 74.4% was documented from studies done in Kolkata and Puducherry respectively (Niranjan *et al.,* 2014; Saha *et al.,* 2014).Although fluoroquinolones are among the most effective drugs in treating UTI, diverse studies have revealed increasing resistance to fluoroquinolones between 74.2% and 86% (Niranjan *et al.,* 2014; Somashekara *et al.,* 2014). Similarly in our study resistance to fluoroquinolones is between 78% (2012) and 74% (2014). This may be due to rampant use of fluoroquinolones as first line empirical therapy in UTI cases.

Piperacillin + tazobactam and Aminoglycosides are consistently showing high resistance percentage over the successive three years. Third generation cephalosporines like ceftriaxone is showing very obvious increasing trend of resistance over the three years ranging from 53% (2012) to 73 % (2014). In a study done in Puducherry ceftriaxone resistance is found to be 71.4% which is quite similar to our study (Niranjan *et al.,* 2014). This may be due to the increasing clinical use of third generation cephalosporins following the resistant strains to fluoroquinolones. There is nearly 100% resistance seen with Tetracyclines and Cotrimoxazole, this is very much similar to a study done in Chandigarh, Punjab hospital (95%) and one done in Kerala and Andhra Pradesh (Somashekara *et al.,* 2014; Mehta *et al.,* 2007). Lowest resistance is seen to imipenem and nitrofurantoin in our study. On one side low resistance is consistently seen over three years, in case of imipenem 11.86% (2012) and 11.36% (2014) while for nitrofurantoin there is a decreasing trend of resistance seen over the three successive years decreasing from 36%(2012) to 18 % (2014).

Low resistance to carbapenems may be explained by lesser use of these injectable drugs till date. Also use of nitrofurantoin in the hospital was limited in the past few years because of narrow spectrum of the drug, which may have led to decreased resistance level to the drug.

In the present study another finding which raises an alarm is about MDR, urinary isolates of *E. coli* show 63 % (2012), 64.54%(2013) and 65%(2014) resistance to Fluoroquinolones, third-generation cephalosporins and aminoglycosides collectively. The rising trend of MDR is seen over the successive years. This is comparable to 76% MDR *E. coli* seen in the study done in Puducherry, India (Niranjan *et al.,* 2014).

In a study of antibiotic susceptibility done in Puducherry, amikacin resistance is 17% (Niranjan *et al.,* 2014). These results are quite different from our study thereby stressing upon the regional differences and importance of surveillance of anti-microbial resistance and suggestion of empirical therapy accordingly.

In this retrospective study, there is no consideration of patients demographic data like age, gender etc., clinical symptoms, complicated versus uncomplicated UTI, which are surely the limitations of this study. On the other hand the large sample size of UTI patients and comparison of three years data are strengths of the study.

CONCLUSION

Our study showed that 65 % of *E. coli* isolates from urine samples were MDR. Because of this a bacterium resistant to one antibiotic is often much more likely to be resistant to second choice of antibiotics, thereby increasing the chances of failure of therapy in UTI. The antimicrobial resistant patterns are constantly evolving and vary from region to region it is a necessity for constant antimicrobial sensitivity surveillance. This will help clinicians to provide safe and effective empirical therapies with minimal therapeutic failures.

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