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Dynamism in Resistance Pattern of *Escherichia coli*-A Drift from Indian Council of Medical Research (ICMR)-Antimicrobial Use Guidelines

V. D. Sathish[1*], Guru Prasad Mohanta[2], Elizabeth Anna Mathew[2] and J. Renga Ramanujam[3]

[1]Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, TamilNadu, India
[2]Department of Pharmacy, Annamalai University, Chidambaram, TamilNadu, India
[3]Department of Microbiology, DR.N.G.P Arts and Science College, Coimbatore, Tamil Nadu, India
**Corresponding author*

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A B S T R A C T

Combating Antibiotic resistance has become a great challenge for clinicians due to inappropriate use of antibiotics. Antibiotics once considered being magic bullet is no more having that title. Recommendation in AMR situation in India by Department of Biotechnology (DBT) and Treatment Guidelines for Antimicrobial Use by Indian Council of Medical Research (ICMR) India emphasized the need for regional surveillance starting from the level of state to an individual hospital has been motivation behind the study. Three hospitals in region of Cuddalore in Tamilnadu (India) have been the source of specimen for isolation of *Escherichia coli* during the period of January to July 2019. Antibiogram reports were collected during the study period and utilized for the study. Among 124 isolates Urine, High vaginal swab, Pus, Serum, Oral swab and Amniotic fluid occupied 81.45% (n-101), 08.06%(n-10), 5.64%(n-7), 2.41%(n-3), 1.62%(n-2) and 0.81% (n-1) respectively. Antibiogram for the *Escherichia coli* isolates revealed 90% of resistance to Cefepime, 68% to Ciprofloxacin, 50% to Tetracyclin, 30% to Meropenem *etc.*, Similarly high percentage of sensitiveness was evident in Cefotaxime (95.94%), Imipenum (95.91%), Piperacillin/Tazobactem (86%), Meropenem (70%) *etc*. On comparison with the 2014 ICMR (Antimicrobial Susceptibility) data percentage of resistance and susceptibility has a drastic change both in resistance and sensitivity. From the study it is clear that the generic recommendations on antibiotic use at national level can't be a desirable solution or recommendations to clinicians. The study signifies the importance of local surveillance and infection control programs.

Introduction

E.coli is a gram negative, facultative anaerobic, rod shaped and coliform bacteria responsible for wound infection, food poisoning, lower urinary tract infection, upper urinary tract infection, septicemia, peritonitis, mastitis and pneumonia. In hospital community acquired infections UTI plays significant role due to use of catheters and administration of immunosuppressive drugs in extended hospitalization in extreme clinical

conditions (Lim *et al,* 2017) (1). All the studies related to E. coli have consistently confirmed its dominance in urine samples than other specimens.

Urinary tract infection (UTI) affects part of the urinary tract. If it affects the lower urinary tract it is named as a bladder infection (cystitis) and upper urinary tract it is known as kidney infection(pyelonephritis) (Flores *et al,* 2015) (2). The most predominant causative agent of infection is *Escherichia coli*, although the other bacteria may rarely be responsible. Female anatomy, sexual intercourse, diabetes, obesity, and family history are the responsible risk factors. UTIs are treated with a short course of antibiotics such as nitrofurantoin or trimethoprim/ sulfamethoxazole (Salvatore *et al,* 2011) (3).

In the last two decades, it is challenging to treat UTI infections caused by bacterial pathogens particularly that are transmitted in hospitals, because they are becoming resistant faster than we could develop new antibiotics. At present we have to depend on using toxic medications with potential and serious side effects due to the limitation that they are the only options available to treat infections from the multi-drug resistant bacteria (Wainwright and Milton 1989) (4).Lack of effective antibiotics is as serious as threat to security that will end in more mortality and sudden disease outbreak. Quick emergence of resistant bacteria/infections has again become a threat.

There are evidences in a study by Kalapana *et al,* (2001) (5) in United States of America that the resistance by Escherichia coli to trimethoprim-sulfamethoxazole differed from region to region with a difference of 12% from 22% in western region to 10% in northeast region. In this study we have limited our surveillance within the region of Cuddalore-Tamilnadu (India) for knowing the resistance pattern of *E. coli* from different clinical specimens and comparing with ICMR guidelines as a point of reference.

Materials and Methods

Two hundred clinical samples like Urine, High vaginal swab, Pus, Serum, Oral swab and Amniotic fluid were collected in three private hospitals in Cuddalore and were streaked in selective media EMB agar (Hi-Media) for isolation and identification of *E.coli*. Green Metallic sheen colonies were further confirmed for Gram staining, Motility and Standard Biochemical tests like, IMViC, CHO fermentation test, TSI test, Citrate utilization test, Catalase, Oxidase and Coagulase test. After the confirmation the confirmed isolates were inoculated into nutrient broth (Hi-Media) for multiplication. 0.5 MacFarl and standard was ensured for antibiotic sensitivity testing of all the 124 isolates to have $1.5X10^8$ cells/ml (Baker *et al,* 1983) (6).

After multiplying process standardized inoculums of each isolate were inoculated on to Mueller-Hinton antibiotic sensitivity medium (Hi-Media). Finally, all the isolates were tested for these under listed drug discs: Amikacin, Cefepime, Cefotaxime, Ceftazidime, Ciprofloxacin, Gentamycin, Imipenem, Meropenem, Piperacillin/ Tazobactem and Tetracycline. Standard antibiotic discs (Hi Media) were placed into the bacteria inoculated medium. Sterile conditions were taken care during this process. Incubation; waiting period was for 24 hours.

Depending upon the size of the zone, on comparison with the standard chart, and reviewing with guidelines of Clinical Laboratories Standard Institute (CLSI) for Antimicrobial Susceptibility Testing; the isolates were determined whether they are

susceptible, moderately sensitive or resistant. The susceptibility breakpoints for each antibiotic were defined according to Clinical Laboratory Standards Institute (CLSI) guidelines (CLSI, 2011) (7). The susceptibility patterns were recorded under three categories like sensitive, intermediately sensitive/resistant and resistance. Final reports were collected and utilized for the study.

Results and Discussion

From the 200 clinical specimens collected 124 *E. coli* isolates were obtained with more no of isolates from urine sample having high frequency of 81.45 % (n-101). It was followed by high vaginal swab, pus, serum, oral swab and amniotic fluid which are explained in Table 1.

According to Kibret and Abra (2011)(8) highest isolation percentage for *E. coli* was obtained in urine samples 203 (45.5%). In a study by Devanand and Saxena, 2013 (9), among the gram negative isolates from urine sample 61.45% were *E.coli,* out of which 54.90% were isolated from inpatients of hospitals and 45.10% were from the community.

Our study results are in accordance with previous studies with the prevalence of 81.45% clearly indicating the dominance of *E. coli* in urinary tract infections. Ideal results have been reported by Poonam (2012) (10) also. Similarly many studies have reported the prevalence of UTI infections in Women than men indicating the high risk situation for the female inpatients.

In a study by Kibret and Abra in 2011(11) high resistance erythromycin (89.4%), amoxicillin (86.0%) and tetracycline (72.6%) were recorded. Multi drug resistance of 74.6% and increased resistance rates to all antibiotics except ciprofloxacin were also recorded. *E. coli* isolates showed high rate of resistance to erythromycin, amoxicillin and tetracycline. Wani *et al,* (2009) (12) conducted a susceptibility study in *E. coli* clinical isolates and reported higher percentage of resistance to ceftazidime (99.2%), cefotaxime (99.2%) and ceftriaxone (99.5%). Similarly, Rafay *et al,* (2007) (13) the study in tertiary care hospital in Kashmir-INDIA during 1st August 2005 to 31st July 2007, demonstrated 100% resistance of *E. coli* to cephalosporins. Duttaroy and Mehta (2005) (14) the study was done in Medical College Baroda-Gujarath in 2005, reported resistance of *E. coli* up to 75% to cefotaxime, 85% to ceftazidime and 60% to ceftriaxone. Kibret and Abera (2016) (15) the study was aimed at determining ESBL and antibiogram in Enterobacteriaceae isolates from clinical and drinking water sources in Bahir Dar City, Northwest Ethiopia during September 2013 to March 2015.

The antibiogram study of erythromycin, amoxicillin and tetracycline on *E. coli* isolated from UTI patients, and found high rates of resistance to erythromycin (89.4%), amoxicillin (86.0%) and tetracycline (72.6%), respectively.

Complete susceptibility pattern of all *E.coli* isolates from Cuddalore region is found in the Table 2. Resistance to third generation cephalosporins cefepime, cefotaxime and ceftazidine is 90%, 04.05% and 04.00% respectively by our isolates. Resistance to cefotaxime and ceftazidime has been significantly reduced with a reduced difference of 75% by the isolates of Cuddalore region but with increased level of resistance against cefepime with 11% only. The samples chosen for framing ICMR Treatment Guidelines for Antimicrobial Use by ICMR India in 2017 have been hospitals of national significance with more inpatients of extended hospitalization (Jena *et al,* 2013) (16).

Table.1 Showing prevalence of *E. coli* in clinical specimens

S. No.	Name of the Specimen	No of Isolates (*E. coli*)	Percentage of Prevalence (%)
01	Urine	101	81.45
02	High Vaginal Swab	10	08.06
03	Puss	07	05.64
04	Serum	03	02.41
05	Oral Swab	02	01.62
06	Amniotic Fluid	01	00.81

Table.2 Showing the susceptibility pattern of the *E. coli* isolates in reference to susceptibility pattern described in ICMR Treatment Guidelines for Antimicrobial Use by ICMR India in 2017(17)

S.No	Antibiotic	*E. coli* isolates of our study (n-124)						ICMR India
		Sensitive		Intermed		Resistant		National % of Resistance
		N	%	n	%	n	%	
Third and fourth generation Cephalosporins								
01	Cefepime	12	10.00	0	0	112	90.00	79.00
02	Cefotaxime	119	95.40	0	0	5	04.05	80.00
03	Ceftazidime	18	14.66	101	81.33	5	04.00	81.00
Fluoroquinolones								
04	Ciprofloxacine	34	27.27	6	04.50	84	68.18	81.00
Aminoglycosides								
05	Amikacin	78	63.01	46	37.00	o	0	24.00
06	Gentamicin	72	58	5	04.00	47	38.00	46.00
Carbapenems								
07	Imipenem	119	95.91	0	0	5	04.09	18.00
08	Meropenem	87	70.10	0	0	37	30.00	35.00
Tetracyclines								
09	Tetracycline	62	50.00	0	0	62	50.00	64.00
Pecillin								
10	Piperacillin/Tazobactum	107	86.00	5	04.00	12	10.00	43.00

The possibility for extensive consumption of life saving antibiotics would have surely led to increased exposure of pathogen (*E.coli*) to the antibiotics leading to prevalence of multi-drug resistant bacteria in those areas. Empirical treatment based on guidelines as prophylactic measures might be also one of the reason for increased exposure. Another remarkable change that isolates have been more resistant to fourth generation cephalosporins than third generation on head to head study indicating the acquired resistance from extensive usage of fourth generation cephalosporins.

In a study by Tanzina *et al.*, 2016 (18) in Bangladesh where antibiotic sensitivity test on *E. coli* isolates demonstrated that they

were highly sensitive to Amikacin, Gentamycin, Netilmycin, Imipenem, Meropenem, Pipracillin-Tazobactam, Tobramycin, Nitrofurantoin, Azithromycin, Levofloxacin, and Ciprofloxacin.

In our study apart from third generation cephalosporin other group of antibiotics like fluoroquinolones, aminoglycosides, carbapenems, tetracyclines, penicillin have steadily shown drift in reduction of resistance percentage raging from minimum of 05% under carbapenems to maximum of 33% in penicillin group (Piperacillin/Tazobactem), a positive sign to revert back to conventional antibiotics until the sensitivity reaches 100% for the above classes (Mandal *et al.,* 2001) (19). May be the drift in the form of adaptive resistance by *E.coli* to newer generation, costly, life saving and high side effect antibiotics will lead to change in efflux mechanisms and receptor modulations.

In conclusion to develop a nationwide policy in 2017 the susceptibility pattern data of 2014 has been utilized clearly spacing 2015 and 2016. "AMR situation in India by DBT" Govt. of India (20) has searched the PubMed and Google Scholar databases relating to AMR in India, using following terms: "antimicrobial OR antibiotic and resistance and India." The search was limited to the last five years (July 1, 2012, to June 30, 2017) (Sumanth *et al,* 2017) (21). Comparatively it would give a comprehensive picture on nationwide susceptibility pattern but limited to the zones/regions exposed to research centers or institutes only.

The study clearly emphasizes local antimicrobial surveillance from hospital level to combat the major threat (antimicrobial resistance) to mankind. Only by knowing the extent of resistance and sensitivity can appropriate choices of antibiotic can be made.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

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