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Antimicrobial resistance pattern of uropathogenicEsch.coli - A three year retrospective study

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Abstract:*The Multidrug-resistant* Escherichia coli *(MDR* Esch. coli*) has emerged as a major cause of health care associated infections. They hydrolyze all beta-lactam antibiotics including extended-spectrum cephalosporins and carbapenems, not inhibited by serine beta-lactamase inhibitors like clavulanic acid, sulbactam, and tazobactam and are resistant to many antibiotics. UTIs caused by MDR Esch.coliis a cause of concern due to the decreasing clinical treatment protocols. The aim of this study was to determine the type and antibiotic resistance pattern of the urinary pathogens isolated from patients attending a busy tertiary care teaching institute of Malwa region of Punjab. A total number of 29848 urine samples were collected from R.H Patiala and processed in the Department of Microbiology G.M.C Patiala (Jan. 2014 to Dec2016). These isolates were screened for the detection of ESBL and carbapenemase production by the disc diffusion methods. The retrospective data was analysed of 3850 culture positive urine samples out of which 3061 were Esch.coli. Out of 3061Esch.coli, 1113 Esch.coli were Multi Drug Resistant. Out of 1113, 786 (70.6%) isolates were ESBL-positive, 48(21.3%) were MBL positive and 14 (1.0%) were both ESBL and MBL producers by phenotypic methods. The high levels of resistance to different antibiotics showedthat treatment options are limited and that infection control measures remain of high importance. Drug-resistance surveillance is needed periodically by phenotypic method where molecular techniques are not available for implementation of national UTI Guidelines.*

Keywords:*Urinary Tract Infection, Antimicrobial resistance, Multi Drug Resistant, Extended-Spectrum beta-lactamase (ESBL), Metallo-β-lactamases (MBL).*

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I. Introduction

As the world is heading towards post antibiotic era so there is need to discuss the unnecessary use of antibiotics in clinical set up. The antimicrobial resistance pattern of *Esch.coli* in UTIs have been constantly changing due to the continuous development of new resistance mechanisms like the production of extended spectrum beta lactamases or carbapenemases by bacteria and the spread is because of jumping genesi.e Transposons. ESBLs are Class A plasmid mediated β-lactamases capable of conferring bacterial resistance to penicillin's, 1st, 2nd and 3rd generation cephalosporin's and aztreonam (but not to the cephamycins or carbapenems) by hydrolysis of these antibiotics and which are inhibited by β- lactamase inhibitors such as clauvalinic acid. [1,2]

The increase use of carbapenams lead to the emergence of carbapenam resistant bacteria. Two types of carbapenem hydrolyzing enzymes exist, first is the serine –lactamase (having serine at their active site) and second is the metallo- -lactamase (MBL) which requires divalent cations of Zn as cofactors for enzyme activity. Metallo β -lactamase producers belong to Group 3 and can hydrolyze all metallo- -lactams drugs except monobactams. They are not inactivated by β-lactamase inhibitors like clavulanic acid, sulbactam and tazobactam but they can be inactivated by metal ion chelators like ethylene diamine tetracetic acid (EDTA). Uncontrolled use of broad-spectrum antibiotics and poor hospital infection control practices may lead to the spread of these plasmid-mediated resistance among gram negative isolates. [2,3,4]

With the global increase in the prevalence of Multi Drug Resistance in *Esch.coli*, early detection is crucial, the benefits of which include timely implementation of strict infection control practices to prevent hospital acquired infections.[5] Among the simple and cheaper phenotypic methods available for testing ESBL and MBL production are CST, DDST and MHT, which are sensitive and specific. Though molecular techniques are available to detect MDR i.e ESBL and MBL producers, but these are not available at every tertiary care

hospital in developing country like India. [8] The present study was designed to evaluate standard phenotypic methods for detection of ESBL and MBL production among Escherichia coli in UPEC as *it* is the major etiologic agent in causing UTI, which accounts for 75% to 95% of cases.

II.Objectives

This study was undertaken to determine the type and antibiotic resistance pattern of the uropathogenic*Esch coli* and to detect the prevalence of Multi drug resistance among UPEC *Esch.coli* obtained from the patients admitted in the tertiary care hospital.

III.Material and Methods

The retrospective study was carried out in the Departments of Microbiology the period in year 2014, 2015 and 2016. Clinical samples were collected from patients admitted in the tertiary care 1100 bedded Hospital. Urine samples were collected and processed in the Department of Microbiology. These isolates were studied for their antibiogram and detection of ESBls and MBL production in *Esch coli*. These samples were inoculated on blood agar and MacConkey agar and incubated at 37°C for 18–24 hr under aerobic conditions. Appropriate biochemical tests were done to identify the organisms isolated. Antimicrobial sensitivity testing was performed on Mueller-Hinton agar (MHA) plates by Kirby-Bauer disc diffusion method, according to Clinical Laboratory Standards Institute (CLSI) guidelines. The antibiotics used were: ampicillin (10 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), ofloxacin (5 µg), norfloxacin (10 µg), cefotaxime (30 µg), ceftazidime (30 µg), ceftriaxone (30 µg), cefuroxime (30 µg), aztreonam (30 µg), cefoxitin (30 µg), piperacillin/tazobactam (100/10 µg), imipenem (10 µg), meropenem (10 µg), co-trimoxazole (25 µg). All the antibiotic discs and the media were procured from Hi-media, Mumbai, India. *Esch. coli* ATCC 25922 was used as quality control in antibiotic susceptibility testing. The results were interpreted as per CLSI guidelines. Isolates of *Esch.coli* was intermediate or resistant to at least three drugs in the following classes: beta-lactams, carbapenems, aminoglycosides and fluoroquinolones were labelled as multidrug-resistant *Esch.coli*(MDR). Detection of MBL production was done by *Modified Hodge Test (MHT) and* Imipenem (IMP)-EDTA Combined Disk Test (CDT). [9]

ESBL production was tested by double disk approximation test and combined disk method:

Double Disk Approximation Test: Double disk approximation test was performed by using amoxy-clav (20/10µg) + ceftazidime (30µg). The disks were placed 15 mm apart.

Combined Disk Method: Combined disk method was performed using cefatazidime (30µg) and ceftazidime + clavulanic acid (30/10µg). The disks were placed 20 mm apart.

Modified Hodge Test (MHT): The MHT was performed as follows: First of all bacterial suspension of the carbapenem susceptible strain of *Esch.coli* ATCC 25922 was prepared in 5ml sterile saline and turbidity was adjusted to 0.5 McFarland. This suspension was then diluted to 1:10 using sterile saline. A lawn of the *Esch.coli* ATCC 25922 was streaked on a Mueller Hinton agar plate and was allowed to dry 3–5 minutes.A 10 µg meropenem or ertapenem susceptibility disk was placed in the center of the test area. In a straight line, test organism was streaked from the edge of the disk to the edge of the plate. The plate was Incubated overnight at 37 ^{O}C for 24 hours.

Interpretation*:* After 16–24 hours of incubation, the plates were examined for a clover leaf-type indentation at the intersection of the test organism and the *Esch. coli* 25922, within the zone of inhibition of the carbapenem susceptibility disk.

• **MHT Positive***:* Test had a clover leaf-like indentation of the *Esch.coli* 25922 growing along the test organism growth streak within the disk diffusion zone.

• **MHT Negative:** Test had no growth of the *Esch.coli* 25922 along the test organism growth streak within the disc diffusion

Quality Control: The reference strains used as control were *Esch. coli* ATCC 25922 .[17]

IV.Results

In a retrospective study of 3 years, a total of 12848 urine samples from 2014 to 2016 from indoor patients were screened and those yielding *Esch. coli* were included in the study. Out of 12848 urine samples, culture was positive in 3850 (30%) samples. Out of 3850 culture positive urine sample, *Esch.coli* was positive in 3061 (79.5%) samples i.e. 825 (2014), 1003 (2015) and 1233 (2016). Over a period of 3-year period, a total of 3061 positive *Esch. coli* were analyzed. As expected, *Esch. coli* was the most frequent isolate throughout the three years (average of 79.5 % of the total isolates). Antibiotic susceptibility records as well as the percentage of ESBLs and MBL producers were noted.

Esch. coli [n= 1113 (36.3%)] whichwere found to be resistant to penicillins, cefotaxime and ceftazidime were tested for ESBL production by DDST and CDT. The isolates [n=225 (3.8%)] which

wereresistant to penicillins, 1st generation, 2nd generation, 3rd generation cephalosporin's and carbapenams were tested for MBL production by MHT.

Out of 1113 resistant *Esch.coli*, 786 (70.6%) isolates were ESBL-positive. Out of 786 ESBLs, 41% (n=325) were from ICU, 31% (n=241) were from Surgery Department, 14% (n=110) patients were from Gynae Department 14% (n=110) patients were from Medicine Department.

A total of 225 (3.8%) isolates which showed distorted carbapenem inhibition zones, indicating production of MBLs. These organisms were resistant to cephalosporin's, aminoglycosides, quinolones, piperacillin-tazobactum combination. Out of the 225 imipenem resistant strains, 48 (21.3%) came outto be MBL producer. Location-wise distribution of MBL showed that 26 (54.1%) isolates were from the ICU, 22 (45.9%) isolates were from the post-operative patient (Table-2).

MDR *Esch. coli* showed 100% resistance to Penicillin's and 1st generation, 2nd generation and 3rd generation cephalosporins. 54.7% ofESBL producers were resistant to fluoroquinolones, 36% to gentamicin. Year wise analysis of three consecutive years showed lesser degree of resistance to imipenem(1.7%), amikacin(20.8%), piperacillin + tazobactem (26.9%) and nitrofurantoin (27.8%) . However the drug of choice for these MDR was aztreonam and imipenem (Table1).

Table 1: Antimicrobial Resistance Pattern (%Age) of *Esch.coli* From Urine Samples

Name of antimicrobial agent	**Esch coli 825 (2014)**	**Esch coli 1003 (2015)**	**Esch.coli 1233(2016)**	**Total 3061**
Ampicillin	736 (89.2%)	904 (90.1%)	1121 (91%)	2761(90.1%)
Amoxy –clav	626 (75.8%)	813 (81%)	1044 (85%)	2483(81.1%)
Amikacin	157 (19%)	192 (19.1%)	243 (19.7%)	592 (19.3%)
Gentamicin	165 (20%)	222 (22%)	262 (21.2%)	649(21.2%)
Ciprofloxacin	355 (43%)	443 (44%)	552 (45%)	1350(44.1%)
Levofloxacin	365 (44.2%)	443 (44%)	562 (46%)	1370(44.8%)
Ofloxacin	349 (42%)	437 (43.6%)	562(46%)	1348 (44%)
Norfloxacin	349 (42%)	433 (43%)	552 (45%)	1334(43.5%)
Cefatzidime	510 (61.8%)	628 (62%)	764 (62%)	1902 (62.1%)
Cefuroxime	510(61.8%)	628 (62%)	764 (62%)	1902 (62.1%)
Cefotaxime	512 (62%)	628 (62%)	766 (62%)	1906 (62.2%)
Ceftrioxane	510 (61.8 %)	630 (63%)	786 (63.7%)	1926 (62.9%)
Piperacillin+ Tazobactem	135 (16.4%)	198 (19.7%)	246 (20%)	579 (19%)
Nitrofurantoin	135 (16.4%)	190 (18.9%)	248 (20%)	573 (18.7 %)
Cotrimoxazole	655 (79.3%)	813 (81 %)	988 (80%)	2456 (80.2%)
Imipenem	46 (5.5%)	75 (7.5%)	104 (8.4%)	225 (7.3%)
Meropenam	46 (5.5%)	75(7.5%)	104(8.4%)	225(7.3%)

Table 2. In vitro antimicrobial resistant pattern (%age) of multidrug resistant Esch coli (n=786)

Name of the Antibiotic	**2015 N=216**	**2014 N=264**	**2016 N=306**	**Total N=786**
Amikacin	42 (19.4%)	55(20.8%)	67 (21.8%)	164 (20.8%)
Gentamicin	44 (20.4%)	104 (39%)	134 (41%)	282(36%)
Ciprofloxacin	126 (47.7%)	126 (47.7%)	178 (55%)	430(54.7%)
Piperacillin + Tazobactum	53 (24.5%)	73 (27.6%)	86 (28%)	212(26.9%)
Nitrofurantoin	54 (20%)	54 (20%)	111(36.2%)	219(27.8%)
Imipenem	2(0.9%)	5 (1.8%)	7 (2.2%)	14(1.7%)
Meropenam	2 (0.9%)	5 (1.8%)	7 (2.2%)	14(1.7%)
Aztreonam	Nil (0%)	2 (0.07%)	2(0.6%)	4(0.05%)

Table 3: Prevalence of ESBLs andcarbapenemases in Esch.coli isolated from urine samples (N - 3061)

Total Esch.coli isolates	ESBL Producers		Carbapenemase Producer		Both ESBL and MBL producers N=1338
	Number	ESBL Producers	Number	MBL production by MHT	
3061	1113 (36.3%)	786 (70.6%)	225 (7.3%)	48(21.3%)	14 (1.0%)

Table 4 : Location wise distribution of MBL producing Esch.coli isolates

Name of the ward	Number	% age
ICU	26	54.1%
Surgery	11	22.9%
Ortho	11	22.9%
Total	48	100%

V.Discussion

The increase prevalence in the multi drug resistance Esch.coli is a major cause for concern. β-lactams drugs have been the mainstay of treatment for urinary tract infections. Metallo-β-lactamases (MBL) have recently acquired as one of the most worrisome resistance mechanisms owing to their capacity to hydrolyze all β-lactams, including carbapenems.

Resistance to antimicrobial agents has been noted since the first use of these agents and is an increasing world-wide problem. The increasing and rapid spread of MDR *Esch. coli* constitutes a serious threat to public health worldwide. The current study showed high levels of resistance to the commonly prescribed antibiotic agents like penicillin (92.3%), co-trimoxazole (80%), cephalospoirins (62.5%). ciprofloxacin (44.1%) and norfloxacin (43.5%). Therefore these antibiotics cannot be used as empirical therapy for urinary tract infection. On the other hand very low levels of resistance were detected to antibiotics such as piperacillin -tazobactum (19%), amikacin (19.3%), nitrofurantoin (18.7%) and to carbapenem (7.3%). The comparable rate of antimicrobial resistance has been reported for these drugs in previous studies done in other parts of India and overseas. [18, 19,20,21,22,23] Low resistance was observed for these drugs because they are relatively expensive in price compared to others. Thus, these drugs could be considered as alternative options in the empirical treatment of UTIs.

The present study indicated a high incidence of ESBLs (70.6%) and MBL (21.3%) producing *Esch. coli* in urine samples which isquite similar to the study done at a tertiary care hospital in New Delhi who reported (80%) incidence of ESBL and (10%) incidence of MBL among *Esch.coli* from various clinical samples. [19] Several recent studies from other parts of Asia also demonstrated increasing incidence of ESBL and MBL production in *Enterobacteriaceae*isolates causing UTIs.[22,23,24] In our hospital setting, extended spectrum beta-lactamases production and MBL in *Esch. coli* isolates rising gradually due to uncontrolled prescription of antibiotics.

In this study, there is nearly 100% resistance rates of MDR *Esch. coli* isolates to the first-line oral antimicrobial agents such as amoxicillin, cefuroxime, trimethoprim sulfamethoxazole, tetracycline nalidixic acid and amoxicillin-clavulanate. Esch. coli isolates found to be resistant to amoxicillin-clavulanate between 73% (2014) and 84%(2016). Such high level of resistance of 70% and 74.4% was documented from studies done in New Delhi and Puducherry respectively in 2014. [19,20,21,22,23] While the studies done at New Delhi,West Bengal, Chandigarh and Kerala reported 75% to 95% resistance to Tetracycline and cotrimoxazole.[23,24,25,26]

Resistance to fluoroquinolones varies geographically and is an emerging problem in both developed and developing countries. In the present study, MDR *Esch. coli* isolates showed relatively high resistance rates to norfloxacin and ciprofloxacin i.e 72% (2014),78% (2015), and 79% (2016). This may be due to rampant use of fluoroquinolones as first line empirical therapy in UTI cases. Fluoroquinolones are among the most effective drugs so far particularly for urinary tract infection as they can be used orally but now studies done in different regions of India have revealed the increasing resistance to fluoroquinolones between 88.5% , 76% and 72% .[16,17, 26]

In present study the amikacin resistance of MDR Esch.coli is 19.4% in 2014, 20.8% in 2015 and 21.8% in 2016 where as it is almost equal to the study done in Puducherry and New Delhi , where they reported amikacin resistance in 17% and 25.5% of cases respectively. These results are quite different from our study thereby stressing upon the regional differences and importance of surveillance of antimicrobial resistance and suggestion of empirical therapy accordingly.[17,18,19,22]

Of 3061 Esch.coli, 225 (4%) showed imipenem resistance, out of it only 48 (2.9%) were MBL producers. Most isolates were from the intensive care unit and from post-operative patients. Our findings show that there are significant numbers of isolates having MBL production along with multidrug resistance. There is a need for active surveillance to detect MBL producers. Low level of resistance was consistently observed over a period ofthree years, in case of imipenem (7.3%), piperacillin + tazobactam (19%) nitrofurantoin (20%), and aminoglycosides (21%). This 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. [21,22]

The majority of these MDR isolates were from patients admitted in ICU ward (54.1%) and (45.9%) post-operative wards. Use of indwelling medical devices is common in these areas, which can play an important role in the spread of infective agents. These results simulated those of Nandy et al who reported 41.1% MDR producers from the ICU, 29.41% from surgical wards, 11.76%. [24]

VI. Conclusion

Multi drug resistant isolates in a hospital environment poses not only a therapeutic problem but is also a serious concern for infection control management. Therefore, use of carbapenems which is a reserved drug should be restricted to severe infections, especially in critically ill patients, to avoid rapid emergence of resistant strains. Therefore, early detection and prompt instillation of infection control measures is the first step to prevent further spread of pan resistant isolates to other gram negative rods. The effective and highly sensitive phenotypic methods can be employed in any laboratory where molecular techniques are not available to both screen for and toconfirm the presence of this important mechanism of antimicrobial resistance.

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Conflict of Interest

None

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