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ALARMING RATES OF PREVALENCE OF ESBL PRODUCING *E. COLI* IN URINARY TRACT INFECTION CASES IN A TERTIARY CARE NEUROSPECIALITY HOSPITAL

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ABSTRACT

Introduction: Extended spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most beta lactam antibiotics, including Penicillins, Cephalosporins, and the Monobactam, Aztreonam. ESBL strains are on the rise in case of community acquired and healthcare associated infections. Escherichia coli are the most common uropathogen worldwide. Prevalence of ESBL production and their antimicrobial susceptibility patterns in urinary E.coli isolates in a tertiary care Neurospeciality hospital were studied.

Materials and Methods: Urinary *E.coli* isolates were identified and their susceptibility was tested using Vitek2.Isolates were classified as point of admission UTI (POA-UTI), catheter associated UTI (CAUTI), hospital Acquired UTI (HAUTI). Susceptibility analysis was done.

Results: 198 E.coli urinary isolates were obtained between November, 2015 and March, 2017. Out of 87 POA-UTI cases 73.56% were found to be ESBL producers, among which the sensitivity pattern was Ertapenem (81.6%), Piperacillin (57.47%), Amikacin (80.47%), Fosfomycin (97.70%), Nitrofurantoin (82.75%), Ciprofloxacin (17.24%). All the *E.coli* isolates producing CAUTI were ESBL producers, among which the sensitivity pattern was Ertapenem (81.48%), Piperacillin (40.74%), Amikacin (70.37%), Fosfomycin (96.29%), Nitrofurantoin (77.77%), Ciprofloxacin (18.51%). Among other isolates E.coli strains producing HAUTI, the sensitivity pattern was Ertapenem (72.61%), Piperacillin (45.23%), Amikacin (79.76%), Fosfomycin (98.80%), Nitrofurantoin (79.31%), Ciprofloxacin (16.66%).

Conclusion: The strains causing CAUTI are ESBL positive with a limited range of antibiotic susceptibility, possibly due to antibiotic pressure. This shows that irrational use of antibiotics show an increase in ESBL producers. Early institution of antibiotics could be a possible solution to this problem. (BL+BLI) combinations seem to have more usefulness in POA-UTI cases than CAUTI cases. Fosfomycin seems to be a better alternative.

Keywords: ESBL, urinary tract infections, susceptibility testing, Escherichia coli

INTRODUCTION

ESBL-producing *E.coli* is antibiotic-resistant strains of E.coli. Itisa common bacterium which will normally exist innocuously in the gut (intestines). The ESBL-producing strains manufacture an enzyme called extended-spectrum beta lactamase (ESBL). ESBL makes them resistant to cephalosporin antibiotics, as well as a number of other classes of antibiotics - making these infections much more challenging to treat (Nordqvist, 2007). ESBL-producing *E.coli* can cause a wide range of infections, ranging from urinary tract infections to severe sepsis. Infections with ESBL-producing *E.coli* most commonly hit the elderly, people who have recently been in hospital and people who receive or have received antibiotic treatment. The first case of ESBL *E. coli* appeared about four years ago and seemed to infect elderly women. As it has spread, so has the age and type of patient who gets infected. These bacteria cause infection if they get into an area of the body where they are not normally found, such as the urinary tract. Urine infection is the most commonly diagnosed infection, but infection in the lungs (chest), wounds and in the blood can also occur. Infections caused by ESBL-producing bacteria can be more difficult to treat because of antibiotic resistance, as there are fewer effective antibiotics to use (Surrey and Sussex healthcare).

In recent years there has been an increased incidence and

prevalence of extended-spectrum β-lactamases (ESBLs), enzymes that hydrolyze and cause resistance to oxyimino-cephalosporins and aztreonam. The majority of ESBLs are derived from the widespread broad-spectrum β-lactamases TEM-1 and SHV-1. There are also new families of ESBLs, including the CTX-M and OXA-type enzymes as well as novel, unrelated β-lactamases (Bradford, 2001). As with other bacteria, ESBL-producing bacteria can be spread from person-to-person on unwashed hands, on equipment that is contaminated and has not been sufficiently cleaned, or can be picked up from the environment. This can happen both in the community and in hospital. There are a number of factors that make a person more likely to become colonised or infected with ESBL-producing bacteria. These includespatients are more susceptible to infection due to an underlying illness, taking repeated courses of antibiotics a prolonged stay in hospital and having a urinary catheter (Surrey and Sussex healthcare).

Most ESBLs are derivatives of TEM or SHV enzymes (Bush, Jacob & Medeiros, 1995; Jacoby & Medeiros, 1991). There are now >90 TEM-type β-lactamases and >25 SHV-type enzymes. With both of these groups of enzymes, a few point mutations at selected loci within the gene give rise to the extended-spectrum phenotype. TEM- and SHV-type ESBLs are most often found in E. coli and K. pneumoniae; however, they have also been found in Proteus spp., Providencia spp., and other genera of Enterobacteriaceae. The majority of ESBLs contain a serine at the active site and belong to Ambler's molecular class A (Ambler, 1980). Class A enzymes are characterized by an active-site serine, a molecular mass of approximately 29,000 Da, and the preferential hydrolysis of penicillins (Medeiros, Mayer & Opal, 1988). ESBLs contain a number of mutations that allow them to hydrolyze expanded-spectrum β-lactam antibiotics. While TEM- and SHV-type ESBLs retain their ability to hydrolyzepenicillins, they are not catalytically as efficient as the parent enzymes (Bush & Singer, 1989). In addition, the expansion of the active site that allows the increased activity against expanded-spectrum cephalosporins may also result in the increased susceptibility of ESBLs to β-lactamase inhibitors (Jacoby & Medeiros, 1991) ESBLs are not active against cephamycins, and most strains expressing ESBLs are susceptible to cefoxitin and cefotetan.

MATERIALS AND METHODS

Study sample: This study was performed at the Department of Microbiology and Infection Control, Institute of Neurosciences, Kolkata. 198 *E.coli* urinary isolates were obtained from November 2015 to March 2017 from patients (indoor and outdoor) visiting the hospital during this time span.

Sample Collection: Mid stream urine sample was collected from patients without catheters. From catheterized patients urine sample was collected under all aseptic precautions from the sampling port with a sterile syringe.

Method: Patients with symptoms of urinary tract infection (UTI) were screened by routine examination of urine followed by semi-quantitative culture on Chrom-UTI (chromogenic media) and MacConkey agar. Culture plates with 105 CFU/ml were considered for UTI diagnosis. The plate was incubated for 24 hours. Organisms were identified by biochemical tests and confirmed by Vitek 2. Antimicrobial susceptibility testing was performed by Kirby Bauer disc diffusion method on Mueller-Hinton agar. In this method, the inoculums were adjusted to 0.5 Mc-Farland standards and swabbed onto the surface of Mueller-Hinton agar with the help of a swab (Wayne, 2015). The antibiotic discs were placed onto the agar plate and incubated at 37°C for 18 hours. From the cultured organisms E. coli isolates were chosen as per our objective. The following antibiotics discs were used: cefotaxime (30µg)/ cefpodoxime (30µg)/ ceftriaxone (30µg)/ ceftazidime (30µg)/ aztereonam (30µg) and amoxicillin-clavulanate (30µg) for the ESBL producing Escherichia coli on Mueller-Hinton agar. Isolates were tested for minimum inhibitory concentration (MIC) of antimicrobials by Vitek2 automation. Interpretations of the results weredone according to CLSI guidelines (Cockerill, 2011).

RESULTS

A urinary tract infection (UTI) is an infection involving any part of the urinary system, including urethra, bladder, ureters, and kidney.

- POA-UTI – Point of admission UTI - Urinary tract infections acquired within the first two calendar days of admitting the patient.(Table 1, Figure 1 & Figure 2)

• HA-UTI – Hospital acquired UTI - Urinary tract infections acquired from the hospital in which the patient is admitted.(Table 2 & Figure 3)

• CA-UTI – Catheter associated UTI - Among UTIs acquired in the hospital (HAUTI), approximately 75% are associated with a urinary catheter, which is a tube inserted into the bladder through the urethra to drain urine. (Table 3 & Figure 4)

The percentage of ESBL producers found in different forms of observed UTI's was HAUTI - 90.09%, POA-UTI – 73.56%, CAUTI – 100%.

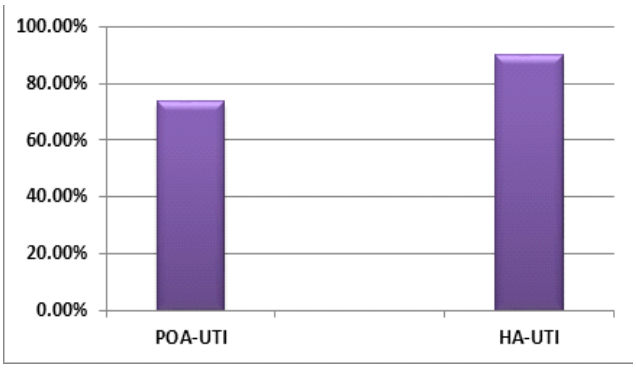

Figure 1: Percentages of ESBL producers in POA-UTI and HAUTI cases

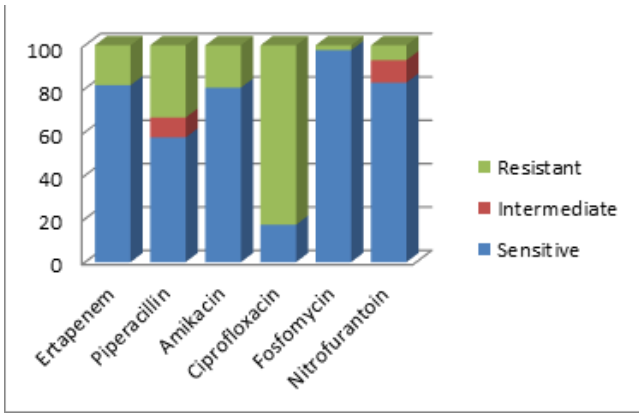

Figure 2: Sensitivity patterns observed in ESBL producing E. coli isolates in POA-UTI cases

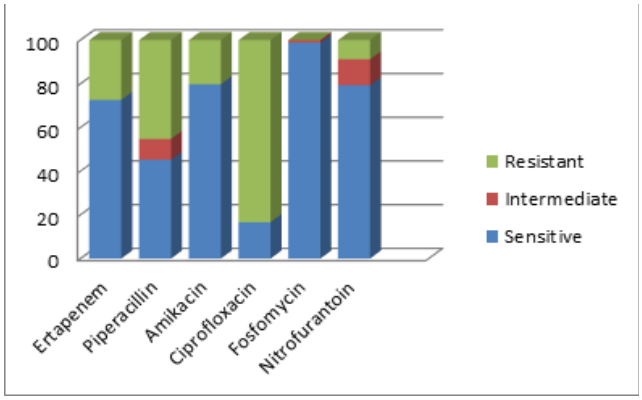

Figure 3: Sensitivity patterns seen in ESBL producing E.coli isolates in HAUTI cases

Table 1: POA-UTI cases

POA-UTI (n=87)						
	Ertapenem	Piperacillin	Amikacin	Ciprofloxacin	Fosfomycin	Nitrofurantoin
Sensitive	81.6%	57.47%	80.45%	17.24%	97.7%	82.75%
Intermediate	-	9.19%	-	-	-	10.34%
Resistant	18.4%	33.34%	19.55%	82.74%	2.3%	6.91%

Table 2: HAUTI cases

HAUTI (n= 84)						
	Ertapenem	**Piperacillin**	**Amikacin**	**Ciprofloxacin**	**Fosfomycin**	**Nitrofurantoin**
Sensitive	72.61%	45.23%	79.76%	16.66%	98.8%	79.31%
Intermediate	-	9.52%	-	-	1.19%	11.9%
Resistant	27.39%	45.25%	20.24%	83.34%	0.01%	8.79%

Table 3: CAUTI cases

CAUTI (n= 27)						
	Ertapenem	Piperacillin	Amikacin	Ciprofloxacin	Fosfomycin	Nitrofurantoin
Sensitive	81.48%	40.74%	70.37%	18.51%	96.29%	77.77%
Intermediate	-	7.4%	-	-	3.7%	22.22%
Resistant	18.52%	51.86%	29.63%	81.49%	0.01%	0.01%

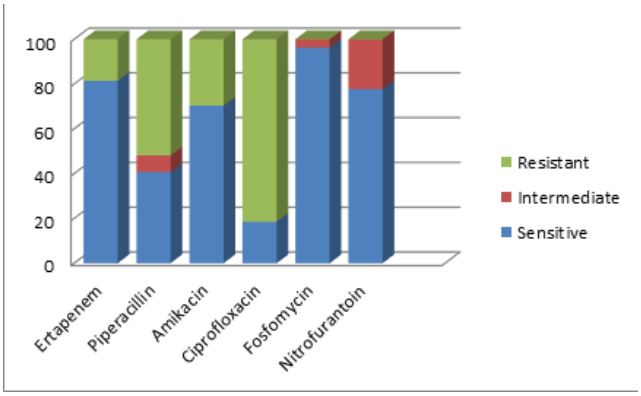

Figure 4: Sensitivity patterns seen in ESBL producing E. coli isolates in CAUTI cases

DISCUSSION

The epidemiology of antibiotic resistant bacteria varies with the type of infection, medical speciality, region, and with time. Development of newer antibiotics counters this to some extent, but often fails as new modes of resistance develop in the bacteria. The most common mode of transmission is through ESBL production (Wagenlehner and Naber, 2006). In the present study of the 198 isolates, the ESBL producers were found in highest percentages in the HAUTI group as compared to the ESBL producers in the POA-UTI group. The subset of HAUTI; the CAUTI group showed all its isolates (100%) to be ESBL producing strains. Out of 87 POA-UTI cases 73.56% were found to be ESBL producers, among which the sensitivity pattern was Ertapenem (81.6%), Piperacillin (57.47%), Amikacin (80.47%), Fosfomycin (97.70%), Nitrofurantoin (82.75%), Ciprofloxacin (17.24%) (Table 1). All the *E.coli* isolates producing CAUTI were ESBL producers, among which the sensitivity pattern was Ertapenem (81.48%), Piperacillin (40.74%), Amikacin (70.37%), Fosfomycin (96.29%), Nitrofurantoin (77.77%), Ciprofloxacin (18.51%) (Table 3). Among other isolates *E.coli* strains producing HAUTI 90.09%, the sensitivity pattern was Ertapenem (72.61%), Piperacillin (45.23%), Amikacin (79.76%), Fosfomycin (98.80%), Nitrofurantoin (79.31%), Ciprofloxacin (16.66%) (Table 2).

ESBL producing organisms were found higher amongst catheterized patients associated with urinary tract infections as compared to non-catheterized patients associated with urinary tract infections. It is suggested that regular screening and surveillance is necessary for ESBL producing organisms. Since ESBLs destroy the cephalosporins that is usually given as a first line antibiotic in hospitals, this leads to increased morbidity and mortality and therefore ESBLs are clinically important (Ashraf *et al.,* 2015). From the above data, Fosfomycin seems to be the ideal drug of choice in case of ESBL treatment in POA-UTI, HAUTI, CAUTI cases, as it shows the highest sensitivity percentage as opposed to Ciprofloxacin and Piperacillin that shows reduced sensitivity percentages in all three groups of UTI's. The duration of catheterization and non-judicial use of antibiotics were also risk factors for the emergence of resistance to drugs and thus treatment of these patients becomes difficult. Administration of antibiotics after thorough screening of these organisms is recommended to prevent the spread of this resistance. Possible solutions could be early institution of antibiotics. Future prospects include an analysis of antibiotic consumption trends.

CONCLUSION

Antibiotic resistance is a problem of deep scientific concern both in hospital and community settings. Rapid detection in clinical laboratories is essential for the judicious recognition ofantimicrobial resistant organisms. The strains causing CAUTI are ESBL positive with a limited range of antibiotic susceptibility; antibiotic pressure seems to be the underlying cause. Proper infection control practices and barriers are essential to prevent spread and outbreaks of ESBL

producing bacteria. As bacteria have developed different strategies to counter the effects of antibiotics, the identification of the resistance mechanism may help in the discovery and design of new antimicrobial agents. Early institution of antibiotics could also be a possible solution to this problem. Beta Lactam + Beta Lactam Inhibitor combinations seem to have more usefulness in POA-UTI cases than CAUTI cases. It was observed that Fosfomycin seems to be a better alternative for this case.

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