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RESEARCH ARTICLE

PREVALANCE OF EXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING UROPATHOGENIC *ESCHERERIA COLI* AND ANTIMICROBIAL SUSCEPTIBILITY PATTERN IN A TERTIARYCARE HOSPITAL IN NORTH INDIA

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ABSTRACT

Background: Urinary tract infections (UTIs) remain the common infections in outpatients as well as hospitalized patients. Extended Spectrum Beta- Lactamase producing organisms causing urinary tract infections (ESBL-UTI) are increasing in incidence and pose a major burden to health care. ESBL-producing E. coli have been isolated from both hospitalized and non-hospitalized patients. Current knowledge on antimicrobial sensitivity pattern is essential for appropriate therapy. The aim of this study was to evaluate the prevalence of ESBL uropathogenic E.coli and the antibiotic susceptibility patterns of ESBL and non ESBL producers, which is essential to guide appropriate antibiotic treatment. **Material and Methods:** Urine samples from 1551 patients received in Department of microbiology, PMC, Patna were processed for wet mount followed by culture and sensitivity. All the samples were inoculated on Nutrient agar, Bood Agar, and Mackoncky Agar. Growth showing significant bacteriuria ($\geq 10^5$ cfu/ml) were further identified by the standard biochemical procedures and antibiotic sensitivity done as per Clinical and Laboratory Standards Institute guidelines. Phenotypic Detection of ESBL and AmpC were performed by combined disc diffusion method as per standard protocol. **Results and observations:** Out of the 1551 processed urine samples 398 (25.66%). samples were culture positive. The total number of *E. coli* isolated were 253 (63.56%). More number of Females 147 (58.10) had significant UTI due to *E. coli* compared with males 167 (41.95%). High level of resistance was seen with Ampicillin 221(87.35%), Cefotaxime 183(72.33%) Ceftriaxone 181 (71.54%), Ceftazidme 175 (69.16%) and Cefepime 167 (66.00%). Resistance to other classes of antibiotics was detected as Ciprofloxacin 191(75.49%), Norfloxacin 203 (80.23%), Cotrimoxazole 201 (79.44%) Nitrofurantoin 133 (52.56%), Gentamycin 121 (47.82%) and Amikacin 79 (31.22%). Among β lactam inhibitors, Amoxyclav 198 (78.26%), Cefoperazone-sulbactam 112 (44.26%). and Pipericillin tazobactam 103 (40.71%). Sensitivity to imipenem was 177(69.96%). No any *E.coli* isolates were resistant to Tigecycline and fosphomycin. (Table 1). MDR isolates represented 173(68.37%). Among these Multidrug resistant strains, ESBLs positive strains were 141 (55.73%) isolates while, the number of AmpC positive strains were 31 (12.25%) isolates. All AmpC producer were co-producers of ESBL, the remaining 113 (44.66%) isolates were pure ESBLs. **Conclusion:** This study highlights the Prevalance of MDR, ESBL and AMP C producers of *E.coli* in UTI. In our study Carbapenems and amkacin are promising drug for ESBL producers while Fosphomycin and Tigecycline use as reserve drug.

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INTRODUCTION

The urinary tract infection is a major worldwide problem. The emergence of multidrug resistant (MDR) has further intensified the existing problem at globally (Shakibaie, 2014). The Extended Spectrum beta lactamase (ESBL) producing bacteria are increasingly causing urinary tract infections. ESBLs have been found most commonly in uropathogens, like *Escherichiacoli* and *Klebsiella pneumoniae*.

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Other enterobacteria and non- fermenting Gram negative baclili also produce ESBLs but to a lesser extent. 2,3 The prevalence of urinary tract infection remains high in women due to particular anatomical specifications. On an average men and women ratio for getting infections with uropathogenic microbial strains and subsequently severe to moderate urinary tract infection estimated 8:1 (Bharti Singh *et al*. 2018; Shigemura *et al*., 2006; Kolawole, 2010; Nithyalakshmi, 2014; Livermore, 2007; Niumsup, 2008). The common symptoms of a UTI are dysuria, urinary frequency, urgency, suprapubic pain and possible haematuria. *etc. E. coli* remain major

uropathogenic microbial strains found in community acquired as well as hospital acquired There are several gram negative bacteria associated with the onset urinary tract infection including *Escherichia coli, Klebsiella species, Pseudomonas species, Proteus species, Enterobacter, Citrobacter* and *Enterococcus species* UTI associated with the onset and progression of the disease. Inappropriate and widespread use of antibiotics has led to the emergence of drug resistance mechanisms like the production of extended spectrum beta-lactamases (ESBL), AmpC beta-lactamases, metallobeta-lactamases and carbapenemases. Various studies have reported the production of ESBL and concomitant multidrug resistance (MDR) among uropathogenic *E. coli* (Hyle, 2005; Mowla, 2011 and Hassan, 2011). This is a serious concern as it affects morbidity, mortility, economic burden and the treatment modalities. Appropriate diagnosis and treatment are always challenging. Therefore it is essential to understand the resistance pattern of the local isolates Current knowledge on antimicrobial sensitivity pattern is essential for appropriate therapy. The aim of this study was to evaluate the prevalence of ESBL uropathogenic E.coli and the antibiotic susceptibility patterns of ESBL and non ESBL producers. The Aim of this study is to identify the current prevalence of MDR and ESBL production among *E. coli* causing UTI in our hospital and to establish a regimen for the empirical treatment of UTI based on the drug sensitivity profile of the isolates in our hospital.

MATERIALS AND METHODS

This prospective study was conducted the Department of Microbiology Patna medcal college and hospital, Patna, india from July 2018 to December 2018. The patient's history with complaint of dysuria, burning micturation, urinary frequency, urgency, haematuria, suprapubic tenderness, pain or pressure in back or lower abdomen was included. Those clinical samples which showed poly-microbial and insignificant growth, incomplete culture form, without proper labeling including date, time, age, lab number and sex were excluded The Mid stream urine (MSU) specimens from 1551 patients sent to the laboratory of Department of Microbiology were received and processed for culture and sensitivity test. Wet mount to detect the presence of pus cells and bacteria was done. The Specimen were inoculated onto Nutrient agar, Blood agar and MacConkey agar and incubated at 37ºC for 24 hours. A specimen was considered positive for UTI if the bacterial colony count is $>10^5$ cfu/ml. They were further processed for identification following standard operative procedures (Collee, 2007). Antibiotic susceptibility test was performed by Kirby Bauer's disc diffusion method using Muller Hinton Agar as per Clinical Laboratory Standards Institute (CLSI) guidelines and susceptibility pattern was noted (CLSI, 2012). The following antibiotic discs (drug concentrations in µg) were used: ceftazidime (30), ceftriaxone (30), imipenem (10) and) were used for Gram negative organisms. Amoxicillin(30), Cefotaxime (30), Cefoperazone (75), Cefipime(30), Cefoperazone-sulbactam (75/30), Piperacillin-tazobactum (10/100), Amoxyclav (30/10), Cotrimoxazole (25), Gentamicin (10), Nitrofurantoin (300), Norfloxacin (10) and Ciprofloxacin (5), Amikacin (10), Tigecycline and fosphomycin (200) Multidrug resistance was defined as resistance to ≥one agent in each of ≥3 categories of antibiotics (Magiorakos, 2012).

Detection of ESBL: Detection of ESBL was done by the combined disc diffusion method using Ceftazidime and Ceftazidime/ clavulanic acid (30/10). An increase in zone size of more than 5 mm was considered as positive for ESBL production (Rice, 2007).

AmpC Detection: Organisms showing resistance to Cefoxitin (zone size <18mm) should be considered as probable AmpC producer and should be confirmed by other methods. Ceftazidime (30µg), Cefotaxime (30 µg) were placed at a distance of 20 mm from Cefoxitin (30µg) on a MHA plate inoculated with test organism. Isolates showing blunting of Ceftazidime or Cefotaxime zone of inhibition adjacent to Cefoxitin disc or showing reduced susceptibility to either of the above drugs and Cefoxitin are considered as AmpC producer (Wayne, 2017).

OBSERVATION AND RESULTS

Out of the 1551 processed midstream urine samples, 398 (25.66%) samples were culture positive. The total number of *E. coli* isolated were 253 (63.56%). More number of Females 147 (58.10) had significant UTI due to *E. coli* compared with males 167 (41.95%). Maximum number of *E. coli* isolated was in the 18-65 years age group163 (64.42%).

Table 1. Antibiotic Resistant pattern of *E.coli* (N= 253)

Antibiotic	No. (%) of resistant isolates
Ampicillin	221(87.35%)
Cefotaxime	183(72.33%)
Ceftriaxone	181 (71.54%)
Ceftazidime	175 (69.16%)
Cefepime	167 (66.00%)
Norfloxacin	203 (80.23%)
Ciprofloxacin	191(75.49%)
Nitrofurantoin	133 (52.56%)
Cotrimoxazole	201 (79.44%)
Gentamycin	121 (47.82%)
Amikacin	79 (31.22%)
Amoxyclav	198 (78.26%)
Cefoperazone/sulbactam	112 (44.26%).
Piperacillin/Tazobactam	103 (40.71%)
Imipenem	177(69.96%).
Fosphomycin	00 (00.00)
Tigecycline	00 (00.00)

Antibiotic susceptibility testing was done for the 253 consecutive non-duplicate *E. coli* isolates. High level of resistance was seen with Ampicillin 221(87.35%), Cefotaxime 183(72.33%) Ceftriaxone 181 (71.54%), Ceftazidme 175 (69.16%) and Cefepime 167 (66.00%). Resistance to other classes of antibiotics was detected as Ciprofloxacin 191(75.49%), Norfloxacin 203 (80.23%), Cotrimoxazole 201 (79.44%) Nitrofurantoin 133 (52.56%), Gentamycin 121 (47.82%) and Amikacin 79 (31.22%). Among β lactam inhibitors, Amoxyclav 198 (78.26%), Cefoperazone-sulbactam 112 (44.26%). and Pipericillin tazobactam 103 (40.71%). Sensitivity to imipenem was 177(69.96%).

No any E.coli isolates were resistant to Tigecycline and fosphomycin. (Table 1). There was a wide spectrum resistance to different antibiotics. MDR isolates represented 173(68.37%) while susceptible strains detected in 80 (31.62%) isolates . Among these Multidrug resistant strains, ESBLs positive strains were 141 (55.73%) isolates while, the number of AmpC positive strains were 31 (12.25%) isolates. All AmpC producer were co-producers of ESBL, the remaining 113 (44.66%) isolates were pure ESBLs (Figure 1). ESBLs positive isolates were found to be more resistant than ESBLs negative isolates to other classes of antimicrobials (Table 2).

Table 2. Sensitivity of ESBL isolates to other antibiotics (n=141)

Antibiotic	Total number of sensitive isolates	Percentage(%) of sensitivity of ESBL Isoates
Ciprofloxacin	18	(12.76)
Norfloxacin	13	(9.21)
Co trimoxazole	9	(6.38)
Nitrofurantoin	34	(24.11)
Gentamycin	57	(40.42)
Amikacin	87	(61.70)
Imipenem	119	(84.39)
Fosphomycin	253	(100)
Tigecycline	253	(100)

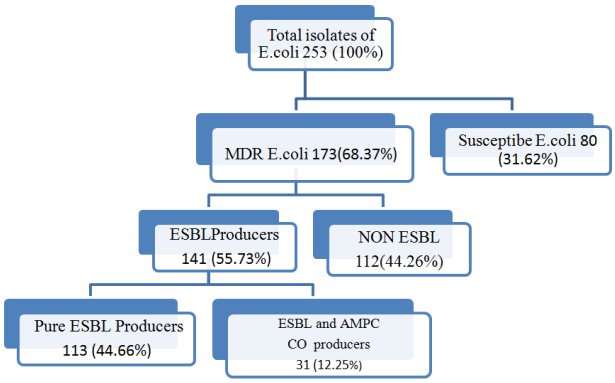

Figure 1. Prevalance of ESBL

DISCUSSION

Urinary tract infections are one of the most common bacterial infection in human population affecting both in community and hospital settings and leads to significant morbidity and health care costs. *E.coli* are the most common pathogens that cause UTIs in both men and women of all age group. The incidence of UTI is more frequent in women than men (Niranjan, 2014). The virulence factors of the organism encompass presence of adhesins, lipopolysaccharide, toxins, iron acquisition, presence of capsules and serum resistance (Cheasty, 2005). Our study showed *E. coli* as the predominant agent accounting for nearly 253 (63.56%). of infections. Shrivastava *et al*. (Shoba Shrivastava, 2018) (68.18%) were in accordance with our study, in which *E. coli* was the predominant. In a study conducted by Rajini *et al et al.,* they stated that *E. coli* account for only 50.1% of UTI cases which was lower than that of our study. That maybe due to the etiological agents of UTI may varies from one locality to another even within the same country (Ranjini, 2015).

In our study Females were more affected 147 (58.10) than male 106(41.89). Similar type of study conducted by Rajini *et al* (Ranjini, 2015) (females (56.9%) and males (43%)) and Yadav *et al*. (2017), (male, 42% female, 58%). All these study showed the higher prevalence of UTI take place in female. As expected as the well known risk factors like shorter urethra, close proximity of the urethra to the perianal region easy contamination with fecal flora, pregnancy and sexual activity predisposes females to UTI. MDR is of special concern in treating UTI. The Isoation rate of MDR E.coli in our study is 173(68.37%) which are comparable to other studies done in India 76.51% (Niranjan and Malini, 2014). A study conducted in Kolkata by Mukherjee *et al*. (Mukherjee, 2013) showed MDR of 92.5% among uropathogenic *E. coli* with more than 80 % resistance to cotrimoxazole and more than 75 % strains resistant to and ciprofloxacin. Similar resistance pattern has been demonstrated in other studies across various countries. Hassan *et al*. (Hassan, 2011) from Karachi had reported 94%, 85% and 60% resistance among urinary *E. coli* isolates to ampicillin, ciprofloxacin and gentamicin respectively while studies by Mowla *et al*. (Mowla, 2011), from Bangladesh showed 92% and 50% resistance to ampicillin and ciprofloxacin. These above data suggest that the problem of MDR is more important in the developing countries, that may be due to Use of antibiotics in self-medication, over the counter availability of antibiotics, animal husbandry, dispensing them without proper prescriptions, non adherence to antibiotic regimen by the patients and indiscriminate use even by clinicians. All may act as contributory factors in the misuse of antibiotics and the subsequent development of MDR in this region. The antimicrobial susceptibility testing showed high level of resistance to different β- lactam antibiotics mainly Ampicillin 221(87.35%), Cefotaxime 183(72.33%), Ceftriaxone 181(71.54%), and Ceftazidme 175 (69.16%). Resistance to other classes of antibiotics was detected as Norfloxacin203 (80.23%), Ciprofloxacin 191(75.49%) Cotrimoxazole 201 (79.44%) and Nitrofurantoin 133 (52.56%). These results were in consistent with that observed in other studies (Niranjan and Malini, (2014); Fody *et al.,* 2017 and Gupta *et al*., 2013).

Our study showed the susceptibility of Imipenem were 177 (69.96%). This frequency was comparable with studies of Yadav *et al* 85.9% . In other study susceptibility varied from 95 - 100% for imipenem (Niranjan and Malini 2014[16]; Fody *et al.,* 2017). ESBL producing bacteria is one of the most important causes of treatment failure, morbidity and prolonged stay in hospitals. The widespread use of antibiotics and selective antibiotic pressure to treat bacterial infections has rapidly increased the emerging multidrug resistance strains specially ESBL producing ones (George M. Eliopoulos and Bush, K). This study was designed to determine the prevalence of MDR, ESBL and AmpC production among strains of uropathogenic *E. coli* isolates. Occurrence of ESBL production in *E. coli* strains is important as they constitute a major part of the commensal flora of the intestines and thus serve as reservoir of infection in the community. A study by Mekki *et al*. (Mekki, 2010) had shown ESBL production among uropathogenic MDR *E. coli* as 53% compared to ESBLs 141 (55.73%) isolates in our study. Our results showed that out of133 (56.11%) ESBL producing *E. coli*, 113 (44.66%) were pure ESBL producers and 31 (12.25%) were both ESBL and AmpC co-producers. This result was in agreement with another study conducted by Gupta *et al.* (2013), who showed that of 52.6% of the isolates were ESBLs producer strains and 10% of strains were AmpC producer. Gupta *et al.* (2013) found that not all AmpC positive strains were co-producer of ESBL and AmpC, but only 8% of the strains were co-producers of ESBL and AmpC, but in our study all AmpC positive isolates were co-producers of ESBL and AmpC. This may be due to variation in place. ESBL producers were more resistant than susceptible strains to classes of antibiotics rather than beta lactams. Resistance to quinolones was recorded to be 203 (80.23%) to norfloxacin and 191(75.49%) to ciprofloxacin. This was in consistent with Gupta *et al.* (Gupta, 2013) and Chander and Shrestha (2013), who reported high level of resistance to quinolones(> 90%). The reason for that is the widespread empirical treatment with quinolones for treatment of UTI in our locality. In ESBL producing strains, Nitrofurantoin. resistance was 107 (75.88%). This relatively high rate of resistance was reported in another studies carried

by Gupta *et al.* (2013), however Chander and Shrestha (2013) stated a lower resistance rate (11.7%). Amikacin was another non beta lactam antibiotic which was used frequently in treatment of UTI. Ranjini, *et al*.[19]found 70.42% Amikacin were sensitive to ESBL strain which are comparable to our study 87 (61.70%).Carbapenems still remains as the antibiotic with high sensitivity in ESBL *E. coli*. the isolates in our study were sensitive to imipenem 119 (84.39). Increased prevalence of multidrug resistant ESBL *E. coli* would lead to an increase in the use of carbapenems. This would have a deleterious effect in that the production of carbapenemases by the bacteria would rise. It would be prudent to restrict the use of carbapenems to cases of complicated UTI or those having sepsis or for patients admitted in the intensive care units as their injudicious use may lead to the spread of carbapenemases and further limit the antibiotic armamentarium.

In this study we found all isolates were sensitive to Tigeccycline and fosfomycin. Caio Fernando de Oliveira *et al* found Overall resistance to carbapenems ranged from 18.7% in 2007 to 19.1% in 2015/2016 and no any isolates resistant to tigecycline n Brazil[32]. In a Indian study Sardar, et a found no resistance against Tigeccyclne and fosphomycin. In general, presence of ESBL trait renders the enzymes susceptible to inhibition by inactivators such as clavulanicacid, sulbactam and tazobactam. Raijni *et al* had suggested the use of beta-lactam/beta-lactamase inhibitors for empirical treatment or deescalating strategy in ESBL *E. coli* bacteremia patients. Combination drugs of beta lactams with beta-lactamase inhibitors like piperacillin/ tazobactum and cefaperazone/ sulbactum are increasingly being used now-a-days in health care set-up especially when nosocomial infections are suspected (Yadav, 2017). In the present study Cefoperazone-sulbactam 112 (44.26%) and Pipericillin tazobactam 103 (40.71%) were resistant to isolates. These CTX-M beta-lactamases are readily inactivated by clavulanate and tazobactam and sulbactam. In contrast, our data shows a high degree of *in vitro* resistance to amoxyclav 198 (78.26%). This suggests the possibility of the existence of other beta-lactam resistant mechanisms. Minimum Inhibitory Concentrations and the genotype of ESBL strains will throw more light in this regard.

Conclusion

This study ndicate that *E. coli* is still the most common bacteria causing urinary tract infection and MDR pattern are widely prevalent. The increased clinical threat of ESBL prevalence is creating significant therapeutic problems. Imipenem and amikacin are most effective and may be prescribed for the treatment of infections caused by ESBL strains Restricting the use of antimicrobial agents will release the selection pressure on the bacteria and a reversal from the antibiotic resistant to sensitive state. Inappropriate use of antibiotics has always been a threat for the emergence of MDR producing β latamases posing a greater threat to community as well as hospital acquired infections. Incidence of β latamases producing enzyme is tremendously increasing hence laboratory detection of these ESBL and AMP C producing strains is becoming more important Therefore it is essential that Every hospital should formulate strategic policy depending upon local hospital antibiogram to curtail the over use of antibiotics its antibiotic and an immediate need to initiatives to reduce their prevalence and there hould be a manual of antibiotic policy of the individual institute. Heigher antibiotics such as Tigecycline and fosphomycin should be used as reserve drug as these are still effective against ESBL producing strains. Antibotics should be used judiously.. Morbidity and mortality rate can be reduced by the rational use of antibiotics, surveillance together with applied to strict hospital infection control policies.

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