

# Prevalence of multidrug resistance and extended spectrum beta-lactamases among uropathogenic escherichia coli isolates in urban tertiary care hospital in north India

Satyendra Narayan Singh<sup>1</sup>, Trinain Kumar Chakraverti<sup>2\*</sup>, Ranjan Kumar Srivastava<sup>3</sup>

<sup>1</sup>Professor and HOD, <sup>2</sup>Tutor, <sup>3</sup>Associate Professor, Department of Microbiology, Patna Medical College, Patna, Bihar, INDIA.

Email: [trinain.chakraverti430@gmail.com](mailto:trinain.chakraverti430@gmail.com)

## Abstract

**Background:** *Escherichia coli* is the most prevalent etiological agent in both community acquired as well as hospital acquired urinary tract infections. Emergence of multidrug resistance (MDR) and ESBL producing *E. coli* causing urinary tract infections (UTI) is a serious concern. The aim of this study was to define the current prevalence of MDR, extended spectrum beta-lactamases (ESBL) production and AmpC producers. **Materials and Methods:** Urine samples from 1251 patients received in Department of microbiology, PMC, Patna were processed for wet mount followed by culture and sensitivity. All the samples were inoculated on to Blood Agar, MacConkey Agar and Nutrient agar and 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 method and AmpC disc test as per standard protocol. **Results and Observations:** Out of the 1251 processed midstream urine samples, 353 (28.21%) samples were culture positive. The total number of *E. coli* isolated were 237 (67.13%). More number of Females 143 (60.33%) had significant UTI due to *E. coli* compared with males 94 (39.66%). Maximum number of *E. coli* isolated was in the 18-65 years age group 164 (69.19%) Antibiotic susceptibility testing was done for the 237 consecutive non-duplicate *E. coli* isolates. High level of resistance was seen with ampicillin 211 (89.02%), cefotaxime 179 (75.5%), ceftriaxone 177 (74.68%), ceftazidime 168 (70.88%) and cefepime 167 (70.46%). amoxycylav 193 (81.4%), ciprofloxacin (78.48%), norfloxacin 189 (79.74%) and cotrimoxazole 187 (78.9%). Nitrofurantoin 133 (56.11%), Gentamycin 123 (51.8%) and Amikacin 69 (29.11%) exhibit moderate resistant against *E. coli* isolates. No any *E. coli* isolates were resistant to Tigecycline and fosfomycin. Sensitivity to imipenem was 210 (88.60%). MDR isolates represented 166 (70.4%) while susceptible strains detected in 71 (29.95%) Among these Multidrug resistant strains, ESBLs positive strains were 133 (56.11%) isolates while, the number of AmpC positive strains were 31 (13.08%) isolates. All AmpC producer were co-producers of ESBL, the remaining 102 (43.03%) isolates were pure ESBLs ESBLs positive isolates were found to be more resistant than ESBLs negative isolates to other classes of antimicrobials. **Conclusion:** This study highlights the Prevalence of MDR, ESBL and AMP C producers of *E. coli* in UTI. In our study Carbapenems and amikacin are promising drug for ESBL producers while Fosfomycin and Tigecycline use as reserve drug.

**Key Words:** Extended spectrum beta lactamases, Multidrug resistant, *Escherichia coli*.

## \*Address for Correspondence:

Dr. Trinain Kumar Chakraverti, Tutor, Department of Microbiology, Patna Medical College, Patna, Bihar, INDIA.

Email: [trinain.chakraverti430@gmail.com](mailto:trinain.chakraverti430@gmail.com)

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## INTRODUCTION

Urinary tract infection (UTI) is a spectrum of disease caused by microbial invasion of the genitourinary tract that extends from the renal cortex of the kidney to the urethral meatus<sup>1</sup>. UTIs account for around 5% of consultations in General Practice and are the second commonest infection diagnosed infectious illness worldwide, with about 150 million diagnosed yearly.<sup>2</sup> Risk factors of UTI include immunosuppression, trauma, foreign body, broad-spectrum antibiotic use, infused body

fluids like saline irrigations and also urinary catheterization<sup>3</sup>. UTI has become the most common nosocomial infection, accounting for as many as 35% of nosocomial infections.<sup>4</sup> Urinary tract infections are one of the major health problem effecting both sex male and female of all age group. The incidence is more frequent in women than men due to squatness of female urethra, dearth of prostatic secretions, easy contamination with fecal flora and pregnancy<sup>5</sup>. The common symptoms of a UTI are dysuria, urinary frequency, urgency, suprapubic pain and possible haematuria. Gram-negative bacilli are the most common pathogens associated with urinary tract infection including *Escherichia coli*, *Klebsiella species*, *Pseudomonas species*, *Proteus species*, *Enterobacter*, *Citrobacter* and *Enterococcus species etc.*<sup>6</sup>. However, considering India and other developing countries *Escherichia coli* being the most prevalent and accounting for 75-90% of UTIs<sup>7</sup>. *E. coli* remain major uropathogenic microbial strains found in community acquired as well as hospital acquired 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, metallo-beta-lactamases and carbapenemases. Various studies have reported the production of ESBL and concomitant multidrug resistance (MDR) among uropathogenic *E. coli*<sup>8-10</sup>. This is a serious concern as it affects morbidity, mortality, economic burden and the treatment modalities. Therefore it is essential to understand the resistance pattern of the local isolates. 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

## MATERIAL AND METHODS

This prospective study was conducted the Department of Microbiology Patna medical college and hospital, Patna, India from January 2018 to June 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 polymicrobial 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 1251 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 Blood agar and

MacConkey agar and incubated at 37°C 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<sup>11</sup>. 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<sup>12</sup>. 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-tazobactam (10/100), Amoxyclav (30/10), Cotrimoxazole (25), Gentamicin (10), Nitrofurantoin (300), Norfloxacin (10) and Ciprofloxacin (5), Amikacin (10), Tigecycline and fosfomycin (200)

Multidrug resistance was defined as resistance to  $\geq$ one agent in each of  $\geq 3$  categories of antibiotics<sup>13</sup>.

**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.<sup>14</sup>

**AmpC Detection:** Organisms showing resistance to Cefoxitin (zone size  $<18$ mm) 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<sup>15</sup>.

## OBSERVATION AND RESULTS

Out of the 1251 processed midstream urine samples, 353 (28.21%) samples were culture positive. The total number of *E. coli* isolated were 237 (67.13%). More number of Females 143 (60.33%) had significant UTI due to *E. coli* compared with males 94 (39.66%). Maximum number of *E. coli* isolated was in the 18-65 years age group 164 (69.19%). Antibiotic susceptibility testing was done for the 237 consecutive non-duplicate *E. coli* isolates. High level of resistance was seen with Ampicillin 211(89.02%), Cefotaxime 179(75.5%) Ceftriaxone 177 (74.68%),Ceftazidime 168 (70.88%) and Cefepime 167 (70.46%). Among  $\beta$  lactam inhibitors, Amoxyclav 193 (81.4%), Cefoperazone-sulbactam 106 (45.56%). and Piperacillin tazobactam 101 (42.61%). Resistance to other classes of antibiotics was detected as Ciprofloxacin (78.48%), Norfloxacin 189 (79.74%), Cotrimoxazole 187

(78.9%) Nitrofurantoin 133 (56.11%), Gentamycin 123 (51.8%) Amikacin 69 (29.11%). No any E.coli isolates were resistant to Tigecycline and fosphomycin. Sensitivity to imipenem was 211( 62.02%). (Table 1). There was a wide spectrum resistance to different antibiotics. MDR isolates represented 166(70.04%) while susceptible strains detected in 71 (29.95%) isolates (Figure 1). Among these Multidrug resistant strains, ESBLs positive strains were 133 (56.11%) isolates while, the number of AmpC positive strains were 31 (13.08%) isolates. All AmpC producer were co-producers of ESBL, the remaining 102 (43.03%) 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)

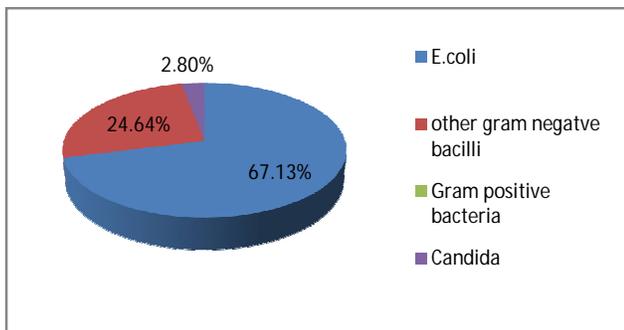


Figure 1: Prevalence of E.coli in UTI

Table 1: Antibiotic susceptibility of E.coli (N= 237)

Antibiotic	No. (%)of sensitive isolates	No. (%) of resistant isolates
Ampicillin	26 (10.97)	211 (89.02),
Cefotaxime	58 (24.47)	179 (75.5)
Ceftriaxone	60 (25.31)	177 (74.68)
Ceftazidime	69 (29.11)	168 (70.88)
Cefepime	70 (29.53)	167 (70.46)
Ciprofloxacin	51 (21.51)	186 (78.48)
Norfloxacin	48 (20.25)	189 (79.74)
Co trimoxazole	50 (21.09)	187 (78.9)
Nitrofurantoin	104 (43.88)	133 (56.11)
Gentamycin	114 (48.10)	123 (51.8)
Amikacin	168 (70.88)	69 (29.11)
Amoxyclav	44 (18.56)	193 (81.4)
Cefoperazone/sulbactam	131 (55.27)	106 (45.56)
Piperacillin/Tazobactam	136 (57.38)	101 (42.61)
Imipenem	210 (88.60)	27 (11.39)
Fosphomycin	237 (100)	00 (00.00)
Tigecycline	237 (100)	00 (00.00)

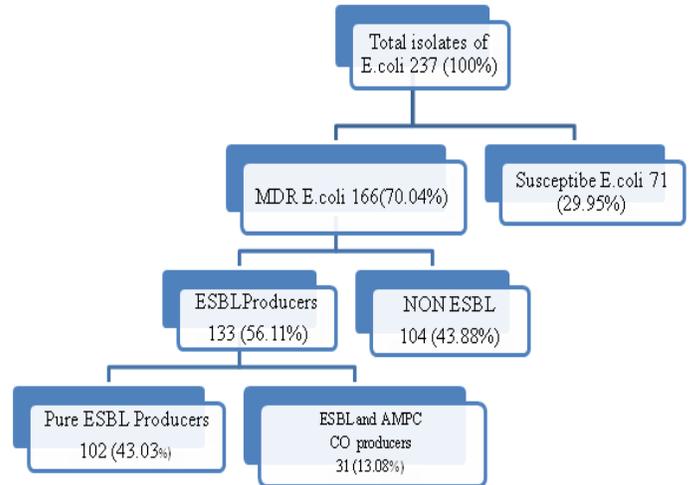


Figure 2: Extended spectrum beta-lactamase (ESBL) detection

Table 2: Sensitivity of ESBL isolates to other antibiotics (n=133)

Antibiotic	Total number of sensitive isolates	Percentage(%) of sensitivity of ESBL Isoates
Ciprofloxacin	18	(13.53)
Norfloxacin	12	(9.02)
Co trimoxazole	8	(6.01)
Nitrofurantoin	29	(21.80)
Gentamycin	53	(39.84)
Amikacin	84	(63.15)
Imipenem	116	(87.21)
Fosphomycin	133	(100)
Tigecycline	133	(100)

None of the ESBL positive strains were sensitive to all the antimicrobial agents tested.

### DISCUSSION

Urinary tract infections are one of the major health problems affecting human both in community and hospital settings. 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<sup>16</sup>. The virulence factors of the organism encompass presence of adhesins, toxins, nlipopolysaccharide, iron acquisition, presence of capsules and serum resistance.<sup>17</sup> Our study showed *E. coli* as the predominant agent accounting for nearly 237 (67.13%) of infections. Shrivastava *et al*<sup>18</sup> (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 indicating that the etiological agents of UTI varies from one locality to another even within the same country<sup>18</sup>. Among 237 isolates, in-patients were 129 (54.43%) and outpatient were 108 (45.56%). This finding is comparable with study of Ranjini CY, *et al*<sup>19</sup>. In our

study Females were more affected 108 (57.5%), than male 79 (42.24). Similar type of study conducted by Rajini *et al.*<sup>19</sup> (females (56.9%) and males (43%)) and Yadav *et al.*<sup>20</sup> (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 166 (70.04%) which are comparable to other studies done in India 76.51% (Niranjan and Malini, 2014)<sup>16</sup>. A study conducted in Kolkata by Mukherjee *et al.*<sup>21</sup> showed MDR of 92.5% among uropathogenic *E. coli* with more than 80 % resistance to and more than 75 % strains resistant to cotrimoxazole and ciprofloxacin. Similar resistance pattern has been demonstrated in other studies across various countries. Hassan *et al.*<sup>22</sup> 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.*<sup>23</sup> 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. 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. MDR can also be due to the spread of certain clonal groups of *E. coli*, which have similar virulence factors and antimicrobial sensitivity patterns.<sup>24</sup> The antimicrobial susceptibility testing showed high level of resistance to different  $\beta$ - lactam antibiotics mainly ampicillin 211 (89.02%), cefotaxime 179 (75.5%) ceftriaxone (74.68), and ceftazidime (70.88%). Resistance to other classes of antibiotics was detected as ciprofloxacin (78.48%), norfloxacin 189 (79.74%), cotrimoxazole 187 (78.9%) and nitrofurantoin 133 (56.11%) and These results were in consistent with that observed in other studies (Niranjan and Malini,<sup>16</sup> 2014.; Fody *et al.*, 2017<sup>25</sup> and Gupta *et al.*, 2013<sup>26</sup>). Our study showed the susceptibility of Imipenem were 27 (88.60%) 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<sup>16</sup>; Fody *et al.*, 2017<sup>25</sup>). 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.<sup>27</sup> This study was designed to determine the prevalence of ESBL and AmpC production among MDR 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. ESBL are generally Ambler class A beta-lactamases that have undergone mutations at critical aminoacids<sup>28</sup>. A study by Mekki *et al.*<sup>29</sup> had shown ESBL production among uropathogenic MDR *E. coli* as 53% compared to ESBLs 133 (56.11%) isolates in our study. Our results showed that out of 133 (56.11%) ESBL producing *E. coli*, 102 (43.03% ) were pure ESBL producers and 31 ( 13.08% ) were both ESBL and AmpC co-producers. This result was in agreement with another study conducted by Gupta *et al.*<sup>26</sup> who showed that of 52.6% of the isolates were ESBLs producer strains and 10% of strains were AmpC producer. Gupta *et al.*<sup>26</sup> 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 121 (90.97%) to norfloxacin and 115 (86.46%) to ciprofloxacin. This was in consistent with Gupta *et al.*<sup>26</sup> and Chander and Shrestha<sup>30</sup>, who reported high level of resistance to quinolones more than 90%. The reason for that is the widespread empirical treatment with quinolones for treatment of UTI in our locality. Another notable resistance was to nitrofurantoin. In ESBL producing strains, resistance was 103 (77.44%). This relatively high rate of resistance was reported in another studies carried by Gupta *et al.*<sup>26</sup>, however Chander and Shrestha<sup>30</sup> 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.*<sup>19</sup> found 70.42% Amikacin were sensitive to ESBL strain which are comparable to our study 84 (63.15%). Carbapenems still remains as the antibiotic with high sensitivity in ESBL *E. coli*. the isolates in our study were sensitive to imipenem 116 (87.21%). 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 our study we found all isolates were sensitive to Tigecycline 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 in Brazil<sup>32</sup>. In a Indian study Sardar, *et al* found no resistance against Tigecycline and fosfomycin. In general, presence of ESBL trait renders the enzymes susceptible to inhibition by inactivators such as clavulanic acid, sulbactam and tazobactam. Rajni *et al* had suggested the use of beta-lactam/beta-lactamase inhibitors for empirical treatment or deescalating strategy in ESBL *coli* bacteremia patients. Combination drugs of beta lactams with beta-lactamase inhibitors like piperacillin/tazobactam and cefepime/sulbactam are increasingly being used now-a-days in health care set-up especially when nosocomial infections are suspected<sup>20</sup>. In the present study 131 (55.27%) of isolates were susceptible to cefepime/sulbactam and 136 (57.38%) to piperacillin/tazobactam. 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 amoxiclav (81.4%). 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. All these above data indicate that a MDR pattern are widely prevalent. Restricting the use of antimicrobial agents will release the selection pressure on the bacteria and a reversal from the antibiotic resistant to sensitive state.

## CONCLUSION

Inappropriate use of antibiotics has always been a threat for the emergence of MDR producing  $\beta$  lactamases posing a greater threat to community as well as hospital acquired infections. Incidence of  $\beta$  lactamases producing enzyme is tremendously increasing hence laboratory detection of these ESBL and AMP C producing strains is becoming more important. Higher antibiotics such as Carbapenem, Tigecycline and fosfomycin should be used as reserve drug as these are still effective against ESBL producing strains. Antibiotics should be used judiciously. Every hospital should prepare depending upon local hospital antibiogram to curtail the over use of antibiotics its antibiotic. 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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