

# ESBLs producing *Enterobacteriaceae* in critical care areas – a clinical and cost analysis from a tertiary health care centre

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## ABSTRACT

**Objective:** ESBLs pose a major threat in clinical therapeutics. In the present study we have tried to do clinical analysis of one hundred ESBLs producing *Enterobacteriaceae* isolates from various clinical specimens from patients admitted in critical care areas. **Methods:** ESBLs detection was done by CLSI, DDS and Vitek methods. Clinical analysis of each patient was done by regularly visiting in CCA and reviewing patient's status and medical records. **Results:** All of the 13 patients on foley's catheter grew ESBLs positive isolates and amongst 10 non catheterized patients, 9 grew ESBLs negative isolates. Thirteen out of 14 patients on CVP/arterial line grew ESBLs positive isolates. Out of 24 patients who underwent surgery, 22 grew ESBLs positive isolate. Forty seven out of 68 patients who were on 3rd or 4th generation cephalosporins within last 1 month of giving the sample grew ESBLs positive isolates. **Conclusion:** We have found a statistically significant ( $p < 0.05$ ) relationship in between foley's catheterization and production of ESBLs from urinary isolates. There was no statistically significant association in between CVP/arterial line and blood culture isolates. We did not find difference in mortality rates in between patients infected with ESBLs positive or negative isolates. The mortality in patients was associated with their primary illness or associated co-morbid conditions. We found that the detection of ESBLs is important for the de-escalation of therapy thereby saving net cost of treatment.

**Key words:** ESBLs; critical care area; *Enterobacteriaceae*

## INTRODUCTION

Beta lactam antibiotics are the mainstay of treatment in our fight against any infection and in any set-up i.e. outpatient or inpatient. A common mechanism of bacterial resistance to beta lactam antibiotics is the production of beta lactamase enzymes. The microbes have even won the beta lactamase stable beta lactams. Extended spectrum

beta lactamases (ESBLs) are the enzymes that mediate resistance to extended spectrum (third generation) cephalosporins and monobactams but do not affect cephamycins or carbapenems. ESBLs pose a major threat in clinical therapeutics. The various risk factors which are found to be associated with infection with ESBLs producing strains include admission to a nursing home, excessive antibiotic exposure (especially to ceftazidime), extended hospital stay, recent surgery, admission to an Intensive care unit (ICU), instrumentation, arterial, venous and urinary catheters.<sup>1-3</sup> There have been various studies which have looked into the prevalence and antimicrobial susceptibility pattern of ESBLs in various organisms in their institutes. Here, we are presenting a study in which we have tried to find out the risk factors and other clinical correlates which are associated with the production of ESBLs in *Enterobacteriaceae* in critical care areas (CCA) i.e. ICU and HDU (High Dependency Units). We have also

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tried to establish the significance of de-escalation therapy in respect with cost-effectiveness.

## MATERIAL AND METHODS

This study was carried out at Indraprastha Apollo Hospitals, New Delhi, India on one hundred *Enterobacteriaceae* isolates from all types of samples (respiratory tract, urinary tract, blood etc) from patients admitted in CCA. This hospital is a big corporate tertiary health care centre where the patients are admitted not only from the surrounding areas but from whole country and abroad. The patients in CCA are usually referred cases from other hospitals. The selection criteria for the strains were (i) Patient had been exposed to CCA for 48 hrs (ii) Repeat isolates of the same organism from the same type of sample within 72 hrs were not taken. (iii) Isolates from consecutive samples obtained that day were not taken (iv) Similar isolates from central venous pressure or internal jugular or intravenous access device and blood cultures, foley's tip and urine culture were not taken into consideration if obtained within 72hrs of each other. Detection of ESBLs was done by phenotypic confirmatory methods i.e. CLSI method [using ceftazidime (30µg) and ceftazidime/clavulanic acid (30/10 µg)], Double disc synergy method [using cefotaxime (30µg) and Amoxicillin/clavulanic acid (20/10µg) discs at a distance of 15mm from centre to centre] and Vitek system (Minimum Inhibitory concentration based-broth microdilution) in *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca*. Clinical analysis of each patient was done by regularly visiting in CCA and reviewing patient's status and medical records. We recorded patient's age, sex, detailed history of present illness, any chronic illness, co-morbidities, any procedure/surgery done, intubation, tracheostomy, duration of ventilator, foley's & CVP line, antimicrobial therapy, duration of ICU/HDU stay, total duration of hospital stay and outcome.

## RESULTS

In our study the median age of the patients with ESBLs positive isolates in critical care areas was 60 years. The total length of stay of patients with ESBLs positive isolates varied from 4 days to 130 days. The length of stay of patients before and after isolation of ESBLs positive *Enterobacteriaceae* varied from 2 to 100 days and 4 to 130 days respectively. The length of stay of patients before and after isolation of ESBLs negative isolates varied from 2 to 125 days and 1 to 164 days.

Forty seven out of 68 patients who were on 3rd or 4th generation cephalosporins within last 1 month of giving the sample grew ESBLs positive isolates. Thirty two patients were not on 3rd or 4th generation cephalosporins but 19 of these grew ESBLs positive isolates. Out of 29 isolates from patients who were on ceftazidime within last 1 month prior to isolation of *Enterobacteriaceae* isolate, 18 were ESBLs positive. Out of 71 patients who were not on ceftazidime within last 1 month before giving the sample, 48 grew ESBLs positive isolates. Out of 74 patients who were on beta lactamase inhibitor combination within last 1 month of giving the sample, 50 grew ESBLs positive isolates. Only 10 out of 26 patients who were not on beta lactamase inhibitor within last 1 month grew ESBLs negative isolates. Out of 19 patients who were on Carbapenems for the last 1 month, 16 grew ESBLs positive *Enterobacteriaceae* isolates and 31 out of 81 patients not on carbapenems grew ESBLs negative isolates. Table 1 shows the percentage ESBL positivity in patients with or without presence of risk factors.

In our study, we found that ESBLs negative isolates were sensitive to ceftriaxone, ceftazidime and cefepime in 19 patients. These patients were on empiric treatment with carbapenems or piperacillin+tazobactam combination. After microbiological culture report, the antibiotics were de-escalated to third generation cephalosporins, thereby

**Table 1: Risk factors analysis of patients with ESBLs positive isolates**

Risk factor	Number of patients with risk factor	Number of ESBLs positive isolates (%) in patients with risk factors	Number of patients without risk factors	Number of ESBLs positive isolates (%) in patients without risk factors
Intubation	40	24 (60%)	10	6 (60%)
Tracheostomy	38	24 (63.15%)	12	6 (50%)
Foley's catheterization	13	13 (100%)	10	1 (10%)
CVP/arterial line	14	13 (92.86%)	6	4 (66.67%)
Neurological disorder	70	46 (65.71%)	30	20 (66.67%)
Diabetes mellitus type-2	37	24 (64.86%)	53	42 (79.24%)
Cardiovascular disorder	22	17 (77.27%)	78	49 (62.82%)
Surgery	24	22 (91.67%)	76	44 (57.89%)

decreasing the financial burden on the patients. The treatment by carbapenems and piperacillin+tazobactam combination amounted to an average of about Rs. 27,052 per patient while the cost of treatment by third generation cephalosporin was about Rs.854 per patient only i.e. a net saving of Rs.26,198.

## DISCUSSION

We found 66% ESBLs positive *Enterobacteriaceae* isolates in our study. ESBLs positivity was seen in 85%, 60.8%, 60% and 66.6% isolates from blood, urinary tract, respiratory tract and pus/wound swabs respectively. We found maximum ESBLs positivity from blood stream isolates. This is in contrast to studies by Shah *et al.* and Coudron *et al.* who reported maximum ESBLs isolates from urinary tract.<sup>4,5</sup> We have also experienced a higher rate (60.8%) of ESBLs producing strains in urinary isolates in our study as compared to other similar studies.<sup>6</sup> It was seen that all the patients who were catheterized grew ESBLs positive *Enterobacteriaceae* isolate from urinary tract specimen. Only 10% of the patients who were not catheterized grew ESBLs positive *Enterobacteriaceae* isolate from urinary specimen. This was significant by chi-square test using continuity correction,  $p=0.000$  ( $p<0.05$ ). Richard's *et al.* and Slucky-Sharga *et al.* also found the association of indwelling catheters with ESBLs positive *Enterobacteriaceae* isolates.<sup>7,8</sup> Whether Foley's catheter provides for a niche to development of ESBLs amongst *Enterobacteriaceae* or whether Foley's was coincidental in being a factor for development of urinary tract infection (UTI) by any organism remains to be answered by more studies. But it is suggested that due to the significant association with ESBLs, indwelling units like foley's should be taken out as soon as their requirement ceases. The higher ESBLs positivity in urinary specimens also emphasizes the high antimicrobial pressure experienced by microorganisms in critical care units. It also signifies the abuse and misinterpretation of this specimen and its culture results. Taking proper precautions, during collection of urine specimen may obviate indiscriminate use of antimicrobials for 'pseudoUTI' like picture which occurs due to colonization associated with catheterization.

We could not find statistically significant association between use of CVP/arterial line and isolation of ESBLs positive *Enterobacteriaceae* from blood stream specimens. Ninety three percent of the patients on CVP/arterial line grew ESBLs positive isolate and 66.7% of the patients not on CVP/arterial line grew ESBLs negative isolate.

This was found to be insignificant by chi-square test using continuity correction,  $p=0.412$  ( $p>0.05$ ).

There was no significant difference in the mortality rates between patients infected with isolates producing ESBLs (45.45%) and patients not infected with isolates producing ESBLs (47.05%). Our patients (both with ESBLs positive and negative isolates) died because of their primary illness or associated co-morbid conditions. This was also corroborated by Emery *et al.* in their study in a tertiary care medical center where they found that there was no significant difference in crude mortality rates between patients infected or colonized with isolates producing ESBLs and patients not infected or colonized with isolates producing ESBLs ( $p=0.14$ ).<sup>9</sup> The ultimate outcome for the patient also depend upon other factors such as actual antibiotic concentration achieved at the infection site, the host immune competence, and non-infectious contributors to morbidity. Carretto *et al.* in Italian intensive care unit found that the overall mortality rate due to ESBLs positive strains was 1% compared to 10.6% caused by ESBLs negative *Enterobacteriaceae* and it was due to association of ESBLs positive *Enterobacteriaceae* isolates with mostly localized infections (wound infections and UTI) in comparison to systemic or severe infections sustained by ESBLs negative strains.<sup>10</sup> It was also found that therapy with carbapenems was started promptly after ESBLs positive isolation (always within 24 hrs. after strain isolation), thus introducing powerful antimicrobials before significant morbidity or mortality could develop. Thus, we can not attribute the mortality in our patients with the isolation of ESBLs producing strains of *Enterobacteriaceae*.

In view of the cost-effectiveness, we strongly recommend the concept of de-escalation of therapy after culture and sensitivity reports are available. Since, the ESBLs positivity rate is high, the choice of empiric treatment amongst beta lactam antibiotics in critical care units should be carbapenems or piperacillin+tazobactam which later on should be de-escalated to after the availability of culture reports.

In conclusion, the presence of ESBLs carries tremendous clinical significance because the antibiotic options for the treatment of ESBLs positive isolates are limited because the plasmids carrying genes for ESBLs also carry genes encoding resistance to other class of drugs. Isolation of ESBLs positive isolates from urine is very strongly associated with foley's catheterization. Also, the detection of ESBLs is important to prevent misuse and overuse of drugs as de-escalation of the antimicrobial therapy

can be done depending upon presence or absence of ESBLs in the isolates. Significant cost factor is involved if appropriately and adequately de-escalated.

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