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Research Article

Clinical profile and outcome of urinary tract infection caused by extended spectrum beta-lactamase producing *Escherichia coli* in critically ill patients in a tertiary care hospital in South India: a case control study

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ABSTRACT

Background: Infections with Extended spectrum beta-lactamase (ESBL) producing organisms have been associated with poor outcome. Our aim of this study is to compare clinical profile of Urinary tract infection (UTI) caused by ESBL producing *Escherichia coli* (*E. coli*) with Non-ESBL producing *E. coli.*
Methods: Retrospective analysis of patients admitted in Intensive care unit in a tertiary care hospital was done. 50 Patients with ESBL producing *E. coli* infection were assigned as cases; 50 Patients with Non-ESBL producing *E. coli* were assigned as controls. Clinical characteristics of UTI caused by both ESBL & non-ESBL producing *E. coli* in critically ill patients and their clinical outcome were observed. Mortality risk on admission was calculated using sepsis scoring system.
Results: Most patients in both groups were in 6th and 7th decade. Male to female ratio in both groups were almost similar. Incidence of complications was higher in ESBL group. Mortality rate was 10% in ESBL group; 4% in Non-ESBL group. Mean duration of ICU stay was 4.2 days (ESBL) and 3.1 days (Non-ESBL). APACHE IV and SOFA scoring system mortality prediction accuracy was 60% in both groups.
Conclusions: Initiation of empirical therapy with carbapenem antibiotics on admission in critically ill with UTI showed significant impact on mortality. Mean duration of ICU stay in ESBL group was longer than non-ESBL group which is statistically significant. Mortality risk was predicted by APACHE IV & SOFA scores on admission with good accuracy.

Keywords: ESBL producing *E. coli*, Urinary tract infection, APACHE IV score, SOFA score

INTRODUCTION

Most common pathogen causing community acquired urinary tract infection (UTI) is *Escherichia coli* (*E. coli*).[1] Due to increased incidence of diabetes mellitus; incidence of UTI is increasing worldwide.[2] Emergence of multi drug resistant strain of *E. coli* is also on the rise due to widespread use of antibiotics. Extended-spectrum beta-lactamases (ESBL) are enzymes produced by micro-organism that confer resistance to most beta-lactam antibiotics including penicillin, cephalosporin, monobactam and aztreonam. Clinical data on outcome of critically ill patients with infection caused by ESBL producing organism is limited. Our aim of this study is to compare the clinical profile of patients with urosepsis caused by ESBL producing *E. coli* with clinical profile of non-ESBL producing *E. coli* in critically ill patients.

METHODS

We conducted a retrospective analysis of medical records of critically ill patients admitted with evidence of urinary tract infection in Intensive care unit of Velammal medical college and research institute, Madurai, Tamil Nadu, India from Jan, 2015 to December, 2015. Patients with following criteria were enrolled for the study:

Inclusion criteria

Patients admitted in medical ICU for critical illness with evidence of urinary tract infection (UTI) with

1. Positive urine culture showing extended spectrum beta-lactamase (ESBL) producing *E. coli* were designated as "*cases*".
2. Patients with non-ESBL producing *E. coli* caused UTI were designated as "*controls*".

Exclusion criteria

1. Patients who are under immunosuppressive therapy or received immunosuppressive therapy in recent past
2. Immunocompromised individual (HIV, Malignancy, Neutropenia)
3. Patient who died within 48 hrs of administering culture sensitive antibiotics
4. Critically ill patients with urine culture showing ESBL organism growth without clinical or imaging evidence of urinary tract pathology (colonizers)
5. Critically ill patients with body fluid culture showing more than one pathogen

Methodology

Among 204 patients with positive urine culture showing significant *E. coli* growth, 130 isolates were ESBL producer and 74 isolates were non-ESBL producer. After careful evaluation of medical records, 50 patients with ESBL producing *E. coli* (cases) and 50 patients with non-ESBL producer (controls) were selected based on above selection criteria. Patients with mortality unrelated to sepsis were excluded from the study.

Clinical data on history, co-morbid conditions, clinical examination, relevant investigations including urine culture and antibiotic sensitivity pattern, imaging features, complications, duration of Intensive care unit (ICU) stay, antibiotic therapy and outcome were collected and compared between two groups. APACHE IV (Acute physiology and chronic health evaluation) and SOFA (Sequential organ failure assessment) score and mortality risk on the first day of admission were calculated in both groups and correlated with clinical outcome and actual mortality. Statistical analysis was done using SPSS software.

RESULTS

Most patients in both groups were in 6th and 7th decade. Mean age was 54 & 58 yrs in ESBL and non-ESBL group respectively. Male to female ratio in both groups were almost similar (ESBL group-1:1.1; Non-ESBL group-1:1.3). Most common symptoms in ESBL group were fever (54%), nausea & vomiting (28%), abdominal pain (20%), altered sensorium (18%), dysuria (16%). Most common symptoms in non-ESBL group were fever (64%), dysuria (36%), nausea & vomiting (32%), abdominal pain (32%), altered sensorium (18%). Antibiotic sensitivity pattern showed universal sensitivity pattern to carbapenem agents in ESBL group. Non-ESBL producers were universally susceptible to amikacin. Incidence of complications was as follows: renal failure (ESBL-62%; Non-ESBL-58%), liver dysfunction (ESBL-28%; Non-ESBL-10%), septic encephalopathy (ESBL-20%; Non-ESBL-16%) and septic shock requiring vasopressor (ESBL-14%; Non-ESBL-8%). Most common complication observed in both group was renal failure. Clinical characteristics of both groups are shown in Table 1.

Multi organ dysfunction syndrome (MODS) was noted in 4 patients in ESBL group; one patient in non-ESBL group. All the patients who developed multi-organ failure syndrome (MODS) did not survive despite effective antibacterial therapy in both groups. Mean duration of ICU stay was 4.2 days in ESBL group and 3.1 days in Non-ESBL group, which is statistically significant (p value- 0.04). Mean duration of antibiotic therapy was 6.5 days in ESBL group which is higher than non-ESBL group with mean duration of 5.8 days. The difference in mean duration of antibiotic therapy between two groups is statistically insignificant (p value-0.06). Mortality rate in ESBL group was 10% which was higher than mortality in Non-ESBL group (4%). This difference in mortality is also statistically insignificant (p value-0.43).

APACHE IV score (on first day of admission) predicted mortality with accuracy of 60% in ESBL group. SOFA scoring system (on first day of admission) showed more than 50% accuracy in predicting mortality in both groups.

DISCUSSION

Incidence of multi drug resistant organisms causing infection is increasing world-wide.[3] In Europe, the Antimicrobial Resistance Surveillance Network (EARS-Net) showed that the proportion of reported *E. coli* isolates resistant to third-generation cephalosporin increased significantly during the 2006-2010 period. In developing countries like India, ESBL producing *E. coli* infection is an emerging problem in health care.

Patients with infections due to ESBL producing organisms have significantly increased morbidity and mortality with longer duration of hospital stay and greater economic burden than do patients without these

infections.[4] Since rectal colonization with virulent strains of ESBL-producing *E. coli* is increasing among healthy individuals, it can be hypothesized that these infections may increasingly occur among patients with no specific risk factors.[5]

Table 1: Comparison of clinical profile of both study groups.

Characteristics	ESBL group (Total-50)	Non-ESBL group (Total-50)	P value
Mean age (yrs)	58.5	54.7	
Gender			
Male	24 (48%)	21 (42%)	
Female	26 (52%)	29 (58%)	
Symptoms			
Fever	27 (54%)	32 (64%)	
Abdominal pain	10 (20%)	16 (32%)	
Vomiting	14 (28%)	16 (32%)	
Burning micturition	8 (16%)	19 (38%)	
Reduced urine output	5 (10%)	5 (10%)	
Co-morbidities			
Diabetes	26 (52%)	24 (48%)	
Hypertension	20 (40%)	17 (34%)	
CAD	9 (18%)	6 (12%)	
CKD	8 (16%)	17 (34%)	
CLD	3 (6%)	0	
CVA	6 (12%)	2 (4%)	
Mean duration of ICU stay (days)	4.2	3.1	0.04
Mean duration of antibiotic therapy (days)	6.5	5.8	0.06
Complications			
Altered sensorium	10 (20%)	8 (16%)	
Renal failure	31 (62%)	29 (58%)	
Hepatic failure	14 (28%)	5 (10%)	0.43
Septic shock	7 (14%)	4 (8%)	
MODS	4 (8%)	1 (2%)	
Mortality	5 (10%)	2 (4%)	
No. of patients with mortality risk>10% on day 1			
Apache IV score	5	1	
SOFA score	7	10	
P value <0.05-significant			

MODS- Multi organ dysfunction syndrome, CAD-coronary artery disease, CKD- chronic kidney disease, CLD- Chronic liver disease, CVA- cerebro vascular accident.

In our case-control study, we compared two groups with almost similar characteristics. Female patients were more in both groups, as urinary tract infection is more commonly seen in female. Nearly 40% of patients presented without fever which was common among geriatric population. Risk factors for acquiring multi-drug resistant infections like recent ICU stay, previous antibiotic use, and invasive procedures were not commonly observed in current study. Diabetes was the most common risk factor found in both groups. Most common complication in both groups is renal failure. It is observed that incidence of complication was found to be higher in ESBL group than non-ESBL group.

Mean duration of ICU stay is more in ESBL group which is statistically significant ($p<0.05$). But mean duration of antibiotic therapy in both groups showed statistically insignificant difference. Similar findings were reported in publication from Philippines in 2003.[6] Many research publications from western world demonstrated significantly higher mortality among patients infected with ESBL-producing strains than among patients infected with non–ESBL-producing strains.[7] In our study, difference in mortality rate among two groups was statistically insignificant ($p>0.05$). This can be explained by the use of early empirical antibiotic therapy with carbapenem group in critically ill, which is an ultimate choice in infection due to ESBL producer. Currently, carbapenem group of antibiotics are the most effective agents against infections caused by ESBL producing organisms.[8-10] A recently published article about the impact of adequate empirical antibiotic therapy on

patients admitted to the intensive care unit with sepsis showed better outcome, even though it did not affect early mortality.[11]

All patients who had multi-organ dysfunction at presentation in both groups expired despite receiving effective antibiotic therapy for more than 72 hrs. In a recent study done in paediatric age group in 2009 showed that MODS at presentation is associated with poor functional outcome and higher mortality.[12] It can be concluded that effective antibiotic therapy after the onset of MODS has poor outcome.

A study conducted in south Indian population (Chennai) in 2010, showed similar results. Mean duration of hospital stay was higher in ESBL group which was similar to current study. Like our study, there was no increased mortality noted in ESBL group compared to non-ESBL group. Antibiotic susceptibility pattern also showed similar pattern with universal susceptibility to carbapenem group.[13]

Another comparative study conducted in a European country (Paris, France), showed no significant increase in mortality between ESBL and Non-ESBL producing *E. coli* causing bacteraemia. Important difference between this European study and our study was inclusion of patients with haematological malignancy and immunosuppressive therapy in European study.[14]

In our study, the mortality risk was assessed on admission using recently developed APACHE IV scoring system and SOFA scoring system. Recent studies showed that APACHE IV is better than its previous version (APACHE II) in terms of mortality prediction in critically ill patients with sepsis.[15] APACHE IV score showed higher mortality risk in ESBL group than Non-ESBL group. Both scoring system have good accuracy in predicting mortality at the time of admission.

There are certain limitations in this study. It is a retrospective study with small number of subjects. Findings of this study are to be confirmed with randomised controlled trial with large number of subjects in future.

CONCLUSIONS

Critically ill patients with Urinary tract infection due to ESBL producing *E. coli* showed significantly prolonged ICU stay when compared to infection caused by non-ESBL producing *E. coli*. In contrast, the duration of antibiotic therapy and mortality rate in between ESBL group and non-ESBL group showed statistically insignificant difference. This study showed that initiation of empirical therapy with carbapenem group on admission in critically ill with UTI showed significant impact on mortality. But patients who had with multi-organ dysfunction syndrome (MODS) on admission, showed poor outcome despite adequate antibacterial therapy and supportive care. APACHE IV and SOFA scores on admission predicted the mortality risk with good accuracy. We recommend the use of early empirical therapy with carbapenem agents for urinary tract infection in critically ill for better clinical outcome.

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