

Original Research Article

The study of risk factors and prognostic indicators in patients with bacteremia due to ESBL producing organisms

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ABSTRACT

Background: There is a growing incidence of extended-spectrum beta-lactamases (ESBL) infections worldwide. ESBL bacteremias have been associated with poor outcomes, higher costs and increased durations of hospital stay. The objective of the study was to identify the risk factors in these patients along with antibiotic susceptibility patterns to help identify the patients with poorer prognosis and in guiding treatment decisions more effectively.

Methods: An observational case-control study conducted in a tertiary care hospital in south India over a duration of 18 months. Cases were defined as an adult in-patient who had infection with blood cultures showing growth of ESBL-producing bacteria. A total of 70 patients were included in the study group and subjected to evaluation to determine the risk factors, prognostic indicators and the antibiotic susceptibility.

Results: The major risk factors for ESBL-bacteremia identified were prior admission, prior antibiotic usage, prior Foleys catheter and the presence of a vascular catheter. Pneumonia as the source of bacteremia and requirement of mechanical ventilation were identified as indicators of poor prognosis. Carbapenems, cefoperazone-sulbactam and piperacillin-tazobactam showed excellent sensitivity against ESBL-bacteremia.

Conclusions: The findings of this study emphasizes the importance of recognizing ESBL-bacteremias in patients with risk factors, so that patients who are at risk to have a worse prognosis can be promptly started on a susceptible antibiotic.

Keywords: Bacteremia, Catheter related infections, ESBL, Mechanical ventilation, Pneumonia

INTRODUCTION

Extended-spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most B-lactam antibiotics. There is a growing incidence of ESBL infections worldwide and epidemics have occurred in many countries since ESBL-producing organisms were first identified in 1983.^{1,2} Infections with ESBL-producing organisms have been associated with poor outcomes, higher costs and increased durations of hospital stay.³⁻⁷ The present study is designed to study the various risk factors in patients

with bacteremia due to ESBL-producing organisms. In addition, an attempt has been made to identify the prognostic indicators in these patients with bacteremias along with antibiotic susceptibility patterns to help identify the patients with poorer prognosis and in guiding treatment decisions.

ESBL infections in South Asia

ESBL infections are being increasingly reported from a number of hospitals in India. In one of the recent studies

in India, Sankar et al, in the year 2012 observed ESBL rates of 46% and 50% in out- and in-patients, respectively.⁸ Investigations from India and Pakistan shows an alarming and rapid increase in the prevalence of Enterobacteriaceae with prevalence rate from 6.9% in a hospital in Varanasi, India, to 18.5% in Rawalpindi, Pakistan.⁹ J Jena et al, in a study conducted at Institute of Medical sciences and a private hospital in Bhubaneswar reported a high prevalence of ESBL's 51.78% particularly among *E.coli* isolates 61.84%.¹⁰⁻¹² Syed Mustaq Ahmed, in a study conducted in 2013 in a south Indian rural medical college hospital in Kerala, concluded that there was a moderate incidence of ESBLs among Gram negative isolates.¹³

METHODS

The present study was an observational case-control study conducted among adult in-patients admitted in a tertiary care hospital in south India. The study was conducted over a duration of 18 months: from September 2012 to March 2014. Institutional Ethical Committee approval was obtained. Cases were defined as an adult in-patient who had bacteremia with ESBL-producing bacteria proved on blood culture. Controls were defined as an adult in-patient who had bacteremia with Non-ESBL producing bacteria proved on blood culture (bacteremias caused by *E. Coli*, *Klebsiella*, *Pseudomonas* and *Enterobacter* were included in this study).

All in-patients of age 18 years or greater admitted in medical wards or ICUs with blood cultures growing ESBL-producing organisms were included in the study. Patients with positive cultures for ESBL but without clinical signs of infection (indicating colonization or contamination); or where the culture was performed in an outside laboratory; or patients who got discharged without completion of treatment were excluded from the study.

A total of 70 patients were included in the case group and a total of 70 patients were included in the control group for risk factor analysis. Information was gathered about prior admissions (due to any reason or any duration of hospital stay), previous antibiotic usage within the last 3 months (patients who have received at least a 48 hour course of any antibiotic within the preceding 3 months), prior vascular catheter and prior Foley's catheter insertion. Antibiotic sensitivity profiles were tabulated for each patient and use of empirical antibiotics and definitive antibiotics was recorded.

Statistical methods

The results were analyzed using Epi info version 7 of CDC Atlanta. The differences between two means were tested using unpaired 't' test (pooled 't' test) and the medians in case of non-normal distributions were tested using Mann Whitney U test, while the differences between proportions were tested using Chi-square test.

Yates correction for Chi-square test was applied in case the expected value in any cell is less than 5. Wherever the chi-square test was inappropriate because of small numbers, Fisher's exact P value was used to find the statistical significance. A two tailed P value was used in all instances and a P value of less than 0.05 is considered statistically significant.

RESULTS

A total of 70 patients were included in the case population and 70 patients were included in the control population and the two groups were found to be similar in terms of age and sex distribution (Table 1). The median duration of hospital stay was 11 days for the cases when compared to 9 days in the controls, the difference being statistically significant ($p < 0.001$ S), indicating that ESBL infections were associated with prolonged hospital stay compared to the infections with Non-ESBL producing organisms.

The organism responsible for majority of the cases was *E. coli* (61.4% in cases and 65.7% in controls). This was followed by *Klebsiella* (24.3% vs 21.4%). *E. coli* was found to be the commonest organism responsible for bacteremias with urinary tract as source (83.7%) while the majority of *Klebsiella* bacteremias had respiratory tract as source (62.5%).

Antibiotic sensitivity profiles were recorded for each of the 70 ESBL isolates. Overall 100% of the strains were sensitive to carbapenems, while 98.6% were sensitive to Cefoperazone- Sulbactam and 97.1% were sensitive to Piperacillin-Tazobactam. Of the aminoglycosides, a significant proportion were sensitive to Amikacin (91.4%) and Netilmicin (82.9%) while only 50% of the strains were sensitive to Gentamicin. A high degree of resistance was noted for quinolones with only 9% of the strains being sensitive. The commonest empirical antibiotics used were Ceftriaxone (40.0%) followed by Cefoperazone- Sulbactam (25.7%) and Piperacillin-Tazobactam (20%). These were followed by Meropenem, Ciprofloxacin and aminoglycosides. The commonest definitive antibiotics used were Cefoperazone-Sulbactam (45.7%), Piperacillin-tazobactam (27.1%), and meropenem (21.4%). Only in two other cases aminoglycosides were used as definitive antibiotics- in one patient it was Amikacin and in another it was gentamicin.

Of the 70 patients in the cases, 50 patients (71.4%) got cured, 12 patients (17.1%) expired and 8 patients (11.4%) got themselves discharged without completion of treatment. The outcome of these eight patients are not known. In the 70 patients of the control group 61 patients (87.1%) got cured. 8 patients (11.4%) expired and 1 patient (1.4%) got himself discharged without completion of treatment.

The prior presence of vascular catheter was found to be higher in ESBL group (22.9%) than in Non-ESBL group (8.6%), and the prior use of Foley catheter was also found

to be higher in ESBL group (14.3%) than in Non-ESBL group (5.7%) and the differences was statistically significant. (Table 1).

Table 1: Background characteristics of the study population (Cases vs Controls).

Characteristics	Cases (N=70)	Controls (N=70)	Odds ratio (95% CI)	P value
Age (Mean±SD)	54.9±14.7	54.5±16.5		
Sex ratio (M:F)	1.2:1	1.3:1		
Prior admission	29 (41.4%)	16 (20.0%)	2.39 (1.15-4.97)	0.018;
Prior antibiotic usage	37 (52.9%)	(21.4%)	4.11 (1.96-8.61)	<0.001
Prior Vascular catheter	16 (22.9%)	6 (8.6%)	3.16 (1.16-8.64)	0.02;
Prior Foley’s catheter	10 (14.3%)	3 (5.7%)	3.72 (1.00-14.2)	0.04;
Duration of prior admission. Median (interquartile range)	9 days (6-10)	5 days (0-7)		<0.001;
Duration of total hospital stay. Median (interquartile range)	Days (8-15)	9 Days (8.5-10)		<0.001;
Duration of ICU stay. Median (interquartile range)	9 days (8.5-10)	5 days (0.0-8.5)		<0.001;
Organisms cultured				
(a) <i>E. coli</i>	43 (61.4%)	46 (65.7%)		
(b) <i>Klebsiella</i>	17 (24.3%)	15 (21.4%)		
(c) <i>Acinetobacter</i>	4 (5.7%)	0 (0%)		
(d) <i>Enterobacter</i>	3 (4.3%)	5 (7.1%)		
(e) <i>Pseudomonas</i>	3 (4.3%)	4 (5.7%)		
Source of infection				
(a) Urinary Tract	43 (61.4%)	40 (57.1%)		
(b) Intra-Abdominal	14 (20.0%)	16 (22.9%)		
(c) Pneumonia	8 (11.4%)	9 (12.9%)		
Other Sites(Abscess)	1 (1.4%)	2 (2.9%)		
(e) Unknown	4 (5.7%)	3 (4.3%)		

The median duration of ICU stay was 9 in ESBL group while the median duration in Non-ESBL group was 5 (p<0.001 S). Higher proportion of patients’ required mechanical ventilation in ESBL group (18.6%) compared to Non-ESBL group (8.6%). Similarly, a higher proportion in ESBL group required inotropes (20.0% vs 12.9%) and component transfusion (28.6% vs 22.9%) compared to Non-ESBL group. However, all these differences were not found to be statistically significant (p>0.05; NS).

A multivariate logistic regression analysis was done for risk factors for the prediction of ESBL production with Medcalc software 10.0 version. Prior antibiotic use (p<0.001 S) and prior vascular catheter (p=0.012 S) were significant risk factors with this analysis (Table 2). Other factors like Foley catheter, prior admission, requirement of ventilation, requirement of inotropes and age more than 65 years were not found to be significant risk factors on multivariate analysis.

ESBL production in itself was found to be a risk factor for poorer outcomes. The proportion of mortality was

found to be higher in ESBL group (17.4%) compared to Non-ESBL group (11.4%). Correspondingly, higher proportion of patients were cured in Non-ESBL group (87.1%) compared to that of ESBL group (71.4%). The differences in the various outcomes between the two treatment groups were found to be statistically significant (p=0.02; 5).

Table 2: Multivariate Logistic Regression Analysis of ESBL production with different variables (Backward elimination model).

Variable	Odds ratio	95% CI of odds ratio	Coefficient	Standard error	P value
Prior antibiotic use	4.32	2.02-9.24	1.46	0.38	<0.001; S
Prior vascular catheter	3.77	1.32-10.7	1.32	0.53	0.012; S

As eight patients were discharged without completion of treatment from the ESBL-group, the adjusted mortality was found to be 19.4% in the ESBL group. The risk factors for poorer outcomes (in-hospital mortality), i.e. prognostic indicators, were analyzed for patients with ESBL-bacteremias in comparison with patients with Non-ESBL bacteremias. The case group outcomes were not known for 8 patients. Outcome was not known for 1 control group patient. These were excluded from this analysis.

The mortality was found to be comparatively higher in ESBL group than in Non-ESBL group in relation to almost all variables studied above but statistically significant difference was observed only with regard to two variables namely 'pneumonia as a source of bacteremia' (P=0.02; S) and 'requirement of mechanical ventilation' (S) (Table 3). Thus the two variables pneumonia as the source of bacteremia and requirement of ventilation are prognostic markers for mortality in patients with bacteremia due to ESBL-producing organisms. The mortality was found to be highest with respiratory (pneumonia) source of infection (62.5%) and least with urinary source (8.6%) among patients with ESBL-producing bacteremias.

Table 3: Prognostic and risk factor analysis for patients with ESBL-bacteremia in comparison with patients with Non-ESBL bacteremia.

Variable	Mortality		*p value
	ESBL group (%) (N=62)	Non-ESBL group (%) (N=69)	
Prior antibiotic	9/33 (27.3)	5/15 (33.3)	0.99; NS
Prior admission	9/25 (36.0)	3/15 (20.0)	0.47; NS
Klebsiella as causative organism	7/17 (41.2)	3/15 (20.0)	0.99; NS
Prior vascular catheter	5/14 (35.7)	2/6 (33.3)	1.00; NS
Foley catheter	4/8 (50.0)	1/3 (33.3)	1.00; NS
Pneumonia as a source of bacteremia	5/8 (62.5)	0/8 (0.0)	**0.02; S
Requirement of mechanical ventilation	11/13 (84.6)	2/6 (33.3)	"0.04; S
Requirement of inotropes	9/13 (69.2)	3/9 (33.3)	0.19; NS

* Due to small numbers, Fisher's Exact test p value was estimated. ** Statistically significant difference

Use of empirical antibiotic that was later found to be inappropriate as per sensitivity report could not be linked to the poor outcomes, though the mortality rate was

higher in these patients (22.6% vs 16.1%) when compared to others. This was probably because of small sample size in the present study. Meaningful outcomes for definitive antibiotics could not be deduced as there was increased usage of one specific antibiotic (beta-lactam / beta-lactamase inhibitor) and there was also non-uniformity in the degree of severity of illness (not assessed in this study) in which the various definitive antibiotics were used.

Table 4: Mortality compared between ESBL AND non-ESBL groups by co morbid illnesses.

Variable	Mortality		P value
	ESBL group (%) (N=62)	Non-ESBL group (%) (N=69)	
Type 2 diabetes mellitus	4/31 (12.9)	7/36 (19.4)	0.56; NS
Hypertension	3/11 (27.3)	0/9 (0.0)	0.21; NS
Chronic liver disease	3/5 (60.0)	0/2 (0.0)	0.43; NS
Chronic kidney disease	0/2(0.0)	0/13 (0.0)	1.00; NS
Ischemic heart disease	1/5 (20.0)	0/1 (0.0)	1.00; NS
Any co-morbid illness	12/48 (25.0)	2/16 (12.5)	0.48; NS

DISCUSSION

ESBL production confers resistance to all the beta-lactam antibiotics. In addition, ESBL encoding plasmids also carry genes which encode resistance to other class of antibiotics such as fluoroquinolones, aminoglycosides and sulfonamides.¹⁴ Thus, limited antibiotic choices are available for the treatment of infections caused by these strains. In these circumstances, it is imperative to quantify the problem and reinforce guidelines promoting appropriate antibiotic use. There are very few reports from India on the prevalence of bacteremia due to ESBL producing organisms among hospitalized patients, their risk factors and treatment outcomes. The risk factors identified were prior hospital admission, prior antibiotic usage and Foley's catheterization. These findings were similar to many of prior studies with methodology similar to ours and some with a different methodology.¹³⁻¹⁸

Risk factors

In this study, prior antibiotic usage was found to be a significant risk factor particularly 3rd generation cephalosporin (37.1%). In a prospective cohort study done in a tertiary care hospital in south India, that included 131 episodes of bacteremia, prior use of 3rd or 4th generation cephalosporins was associated with an increased risk of ESBL production.¹⁹ Wu et al, reported

previous antibiotic use as a risk factor, particularly previous usage of oxy-imino cephalosporins. Our study indicates that recent therapy with antibiotics like cephalosporins should raise the suspicion of the possibility of the isolation of ESBL-isolate from the patient. Whenever the patient presents, an attempt must always be made to take the prior antibiotic history including the duration of usage. This information can be used to prescribe effective empirical therapies at the earliest and also avoid the dissemination of these dangerous bacterial strains in the hospital.

In a retrospective case-control study by Kang et al, the number of antibiotics previously administered was independently associated with blood stream infections caused by ESBL-producing *Klebsiella pneumoniae*.²⁰ Similarly in a study by Quirante et al, recent use of more than two classes of antimicrobials within the last 90 days was also found to increase the risk of ESBL-producing *E. coli* or *K. pneumoniae* blood stream infections by approximately 12 times.²¹

Previous hospitalization was a significant risk factor identified in this study. The probable explanation for this would be the colonization of patients with multi drug resistant organisms during hospitalization. This is particularly true when the patient has been admitted in a long term care facility. Factors related to previous hospitalization have been found to be independently associated with ESBL-producing Enterobacteriaceae blood stream infections in several studies.²²⁻²⁴ Hence, in all the cases, a prior hospitalization history has to be taken and suspicion should be there for the possibility of isolation of ESBL-producing organisms and appropriate empirical therapy instituted. Skippen et al, reported prior admission to ICU as an important risk factor for blood stream infections.²⁵

Furthermore, the analyses done by Skippen et al, showed prior antibiotics usage, hospital stay >15 days and prior admission to the intensive care unit to be independent risk factors for the acquisition of ESBL-producing organisms. A retrospective case-control study in a tertiary care center in New Zealand by Freeman et al, reported the previous total in-patient days to be a significant risk factor.²⁶ Marchaim et al, did a multi-center prospective case control study, in which they opined that, patients with ESBL bacteremia presented more often with higher severity-of-infection indices due to the high virulence of ESBL-producing strains.²⁷ This observation is important to the admitting clinician, in that it suggests that empirical antimicrobial therapy should include coverage of ESBL producers in patients with severe sepsis or multi-organ failure.

Presence of a prior vascular catheter and urinary catheter was a significant risk factor in this study. Lee et al, and Menashe et al, reported the presence of vascular catheter to be a significant risk factor for ESBL-production as did several other studies^{13,15,17,24,28} Other devices identified as

risk factors in individual studies were gastrostomy tubes, biliary drainage catheters, mechanical ventilators and central venous catheters.^{29,30}

Prognostic indicators

ESBL bacteremias were associated with greater mortality when compared with Non-ESBL bacteremias. With regards to source of bacteremia, respiratory source was associated with poorer outcomes and was found to be a significant factor for in-hospital mortality in this study (p=0.02 S). On the other hand urinary tract as the source of bacteremia was associated with best outcomes among patients with ESBL-producing bacteremias. Melzer and Petersen, in their prospective cohort study in a tertiary care center during 2003-2005 assessed the 30 day mortality with respect to risk factors and not defined source of bacteremia was a poor prognostic factor.³¹ Ortega et al, Kang et al, and Wang et al, reported increased mortality associated with pneumonia. This similarity with other studies might be because pneumonia predisposes the patients to poor oxygenation and the bacteremia that occurs with it as a source will be associated with poor outcomes in view of the progression to acute respiratory distress syndrome which further worsens the prognosis. Requirement of mechanical ventilation was associated with significant mortality and also a prognostic factor in this study. Marra et al, . reported the use of mechanical ventilation to be risk factor for increased mortality among patients with ESBL-producing bacteremias.³²

The antibiotic susceptibility pattern of ESBL-producing organisms in the bacteremic cases was also assessed in this study. It was found that susceptibility to imipenem, cefoperazone-sulbactam and piperacillin tazobactam was very good among the isolates in this study. Amikacin and Netilmicin also were viable options for treatment in many cases at least as a combination therapy if not as the single definitive therapy but the susceptibility to quinolones was very poor. In a study done by Sharif VA AR et al, showed a sensitivity of 100% for carbapenems, 95.6% for Cefoperazone- Sulbactam. 92.2% for Piperacillin-Tazobactam. 91% sensitivity for Amikacin.³³ These findings has also been seen in various international studies that reported the carbapenems to have excellent coverage for ESBL- producing organisms.

The drawbacks of the present study were the relatively small sample size studied, the probability of recall bias regarding prior antibiotic use, fact that the patients were not followed up after discharge to rule out any recurrence of infection or re-infection. Also the heterogeneous nature of the case population studied means that results may be difficult to apply to any one sub-group of cases e.g. - the ICU population. Microbiological outcome was also not studied. Further studies would be needed to identify the mode of spread of these infections and also if cefoperazone-sulbactam can be a cost effective alternative to carbapenems. The effect of infection-

control measures or restrictions on antibiotic use on the prevalence of these infections also needs to be addressed in the future studies.

CONCLUSION

ESBL infections are found commonly in medical wards and intensive care units and the majority of the ESBL bacteremias were caused by *E. coli* with urinary tract as the commonest source. Major risk factors for ESBL-bacteremia identified were prior admission, prior antibiotic usage, prior Foleys catheter and presence of a vascular catheter. Pneumonia as the source of bacteremia and requirement of mechanical ventilation were identified as indicators of poor prognosis in the patients with ESBL-bacteremias when compared to the patients with Non-ESBL bacteremias. The present study, to conclude, emphasizes the importance of recognizing ESBL-bacteremias among the various infections, and also helps in identifying the patients who are at higher risk for these infections, and also the prognostic indicators for mortality.

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