DOI: 10.36347/sjams.2017.v05i02.020

Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2017; 5(2B):401-406 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com

Original Research Article

Clinical Profile of Blood Culture Positive Septicemia Due to Extended Spectrum Beta Lactamase Strains in Acute Medical Wards at a Tertiary Care Hospital in South India

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Abstract: Resistant bacteria are emerging worldwide as a threat to the favourable outcome of common infections in community and hospital setting due to widespread use of 3rd generation cephalosporins. Infections due caused by extended spectrum beta lactamase (ESBL) producing organisms have markedly increased the rates of treatment failure and death. Our aim was to study clinical profile of septicemia due to ESBL producing organisms. All cases with septicemia and blood culture positivity due to ESBL producing organisms were recruited. This study was conducted over a period of 2 years. Total 58 patients were included with mean age of 48.93years. The most common source of sepsis was from urinary tract 67.3% and most common organ dysfunction observed was Renal77.6% followed by hepatic 34.8% Respiratory dysfunction 31.1%. DIC24.1% and shock13.8%. Presence of four /more organ dysfunction was significantly with mortality/and among 58 patients, 12 patients expired. Main independent predictors of mortality were APACHE II score >25, presentation with septic shock and presence of organ dysfunctions. Carbapenems were drugs with highest sensitivity 100%, followed by Amikacin and, Pipercilin tazobactum.
Keywords: Blood culture, ESBL, Organ dysfunction, Septicemia, cabapemems, Amikacin

INTRODUCTION:

Resistant bacteria are emerging worldwide as a threat to the favorable outcome of common infections in community and hospital settings. Beta lactamase production by several gram negative and gram positive organisms is perhaps the most important single mechanism of resistance to penicillins and cephalosporins [1].The introduction of the third generation cephalosporins into clinical practice in the early 1980s was heralded as a major breakthrough in the fight against beta lactamases mediated bacterial resistance to antibiotics [2]. And widespread use of third generation cephalosporins is believed to be the major cause of mutations in genes coding for beta lactamases that has lead to the emergence of extended spectrum beta lactamases (ESBLs) [1].

The purpose of this study is to focus on the clinical profile of ESBL strains. It is necessary to know the prevalence of these strains in a hospital so as to formulate a policy of empirical therapy in high risk units.

MATERIALS AND METHODS:

Total of 58 inpatients admitted in acute medical care of Department of general medicine, Nizam's institute of medical sciences, Hyderabad, a tertiary care, and multi-specialty referral center) with clinical suspicion of septicemia and blood culture positivity due to ESBL producing organisms (E.coli, Klebsiella), were taken into the study over a period of 2 year and .

Inclusion criteria:

- Age >12 years
- A patient with clinical suspicion of septicemia and blood culture positivity for ESBL in at least one blood culture bottle.

Exclusion criteria:

- Localized ESBL infection in one system but negative blood culture

Clinical information of the recruited patient was collected regarding symptoms, predisposing factors. Detailed examination of the patient was done and clinical details were noted. Patients were investigated with hemogram, renal function tests, serum electrolytes, arterial blood gas analysis. Blood cultures were sent under aseptic precautions for all cases of suspected septicemia. APACHE II score (acute physiology and chronic health evaluation) in first 24 hours was calculated. Vitex 2 system was used to analyze the blood cultures. Imageology work up was done wherever necessary.

All patients consent was taken and Ethics committee permission was taken before starting the study.

STATISTICAL ANALYSIS:

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters, Chi-square/2x2 Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. 95% Confidence Interval has been computed to find the significant features.

Definitions:

An ESBL septicemia is defined as blood stream infection documented by growth of ESBL organism in at least one blood culture specimen from a patient with clinical suspicion of septicemia.

Septicemia is classified as nosocomial if index blood culture had been drawn >48 hours after admission to our hospital.

Upper urinary tract infection was defined if the patient has clinical symptoms, imagelogical evidence with or without positive culture of urine.

Lower urinary tract infection is defined if the patient has clinical symptoms, imagelogical evidence or positive urine culture. Patient is considered responded if the patient improves in clinical grounds and/ in laboratory parameters

RESULTS:

Demographic characteristics: Total of 58 patients with ESBL septicemia in acute medical wards was studied. Of total 58 patients (Table-1) 44 patients responded, 2 patients left against advice, and 12 patients expired. Out of 58, 46.6% were males, 53.4% were females. In 89.7% of cases E.coli was isolated organism. Only 12.1% of the cases were nosocomial. In most of the cases type II diabetes was the underlying disease Urinary tract was the source of infection in 67.2% of cases. Demographic characteristics of the study population are as follows.

Table-1: Demographic Characteristics of Study Population

Characteristics	Value
Age, mean Yrs+/- SD	48.93+/-14.79
No of male: female	27(46.6%): 31(53.4%)
No of E.coli: Klebsiella*	52(89.7%): 5(8.6%)
APACHE score mean	20.84
No of nosocomial infections	7(12.1%)
No with septic shock	12(20.7%)
No with type II diabetes	31(53.4%)
No with chronic kidney disease	12(20.7%)
No with malignancies(includes hematological and non-hematological)	6(10.3%)
No with chronic liver disease	5(8.6%)
No with neutropenia	3(5.2%)
No with HIV	2(3.4%)
Source of sepsis Urinary tract Pancreatico biliary tract	 39(67.2%) 2(3.4%)

*In one case both E.coli & Klebsiella were isolated.

The most common organ dysfunction was renal failure (77.6%) followed by hepatic dysfunction(34.5),respiratory dysfunction(31.1%), DIC(24.1%) and shock(13.8%).The group with respiratory dysfunction included acute lung injury, type I respiratory failure and ARDS. Mean age (Table-2) was more in no survivors group compared to survival (53.83±16.64 Vs 48.41±14.01) but it was not

statistically significant (0.258). The mean hospital stay was more in survival group. The sensorium of the patient at admission (calculated by Glasgow coma scale) was low in no survivors (mean 12.83±3.93) when compared with survivals (mean 14.86±0.63) and it was statistically associated with poor outcome (p value-0.001). The total leukocyte count was elevated more in no survivors (mean 17426.81±9826.9) compared to survivors (mean 12882.27±7953.8), however it was not statistically significant (p value 0.101). Presence of metabolic acidosis was associated with poor outcome (p value-0.001).

Table-2 Mean Values Variables Studied In Survived and Non-Survived

Study variables	Non-Survived(n=12)	Survived (n=44)	P value
Age in years	53.83±16.64	48.41±14.01	0.258
Duration of hospital stay in days	11.67±10.78	15.52±7.70	0.169
Duration of symptoms in days	10.67±9.71	16.16±23.46	0.434
Sensorium (GCS)	12.83±3.93	14.86±0.63	0.001**
RR(r/min)	26.25±8.22	24.84±6.52	0.533
PCV	27.35±7.81	28.92±7.28	0.517
WBC(/mm 3)	17426.81±9826.9	12882.27±7953.8	0.101
Serum Creatinine(mg/dl)	4.65±2.60	3.32±2.63	0.123
Na+(meq/L)	131.33±10.96	130.36±9.77	0.768
K+(meq/L)	4.78±1.09	4.48±0.97	0.348
ABG-Ph	7.25±0.16	7.36±0.08	0.001**
Pao2(mm Hg)	89.80±45.14	88.21±24.01	0.869
APACHE II score	27.75±8.06	19.32±6.04	<0.001**

Table-3 Sensitivity Pattern of Antibiotics:

Class	Antibiotics	Number of patient (n=58)	Percentage (%)
Carbapenem	-	58	100.00
Piperacillin/ tazobactam	-	41	70.7
Ticarcillin/ clavulanic acid	-	6	10.3
Aminoglycosides	Amikacin	44	75.9
	Gentamicin	15	25.9
	Tobramycin	7	12.1
	Netilmicin	1	1.7
Quinolones	Ciprofloxacin	0	0.0
	Levofloxacin	1	1.7
	Ofloxacin	0	0.0
Cotrimoxazole	-	19	32.8
Chloramphenicol	-	7	12.1
Cefepime	-	0	0.0

Carbapenems (Table-3) are the drugs with 100% sensitivity in all cases. Piperacillin/tazobactam was sensitive in 70.7% of cases. Other beta-lactamase inhibitors like Ticarcillin/Clavulanic acid and Amoxicillin /Clavulanate were sensitive in 12% of cases. Among the Aminoglycosides Amikacin has highest sensitivity (75.9%) followed by Gentamicin (25.9%), Tobramycin (12.1%) and Netilmicin (1.7%). All cases had resistance to Quinolones except in one case where Levofloxacin was sensitive.

There(Table-4) was no significant difference in outcome between the survivors and no survivors with respect to the age, gender, type of infection, whether community acquired/ nosocomial, predisposing factor and the type of organism isolated. APACHE II score > 25 was associated with poor outcome and it was statistically significant (p value<0.001). Though the most common source of organism was from urinary tract it was not significantly associated with poor outcome (p value 0.154). Source of infection from pancreatico biliary tract was significantly associated with poor outcome (p value< 0.043).

Among the organ dysfunctions those who had respiratory dysfunction, DIC and shock were significantly associated with poor outcome (p values 0.001, 0.006, <0.001 respectively). Though renal failure was present in all patients (100%) in no survivors group, it was not statistically significant (p

value 0.097). All patients who had four or more organs dysfunction were in no survivors group and presence of four / more organ dysfunctions was significantly associated with poor outcome (p value <0.001).

Table-4: evaluation of study variables in survival and non-survival patients

Study variables		Non-Survived(n=12)	Survived (n=44)	P value
Age in years	<60	8(66.7%)	35(79.5%)	0.443
	>60	4(33.3%)	9(20.5%)	
Gender	Male	6(50.0%)	19(43.2%)	0.750
	Female	6(50.0%)	25(56.8%)	
Type of Infection	CAI	11(91.7%)	39(88.6%)	1.000
	Nosocomial	1(8.3%)	5(11.4%)	1.000
Predisposition	HIV	0	2(4.5%)	1.000
	Steroid Use	1(8.3%)	3(6.8%)	1.000
	Neutropenia	0	3(6.8%)	1.000
	Malignancies	1(8.3%)	4(9.1%)	1.000
	CKD	4(33.3%)	8(18.2%)	0.263
	CLD	2(16.7%)	3(6.8%)	0.289
	Type II DM	5(41.7%)	26(59.1%)	0.338
APACHE II score	<25.0	3(25.0%)	37(84.1%)	<0.001**
	>25.0	9(75.0%)	7(15.9%)	
Microorganisms	E.coli	11(91.7%)	40(90.9%)	1.000
	K.pneumoniae	1(8.3%)	4(9.1%)	1.000
Source of infection	Upper urinary tract	3(25.0%)	11(25.0%)	1.000
	Lower urinary tract	3(25.0%)	22(50.0%)	0.191
	Pancreatico biliary tract	2(16.7%)	0	0.043*
	Unknown	4(33.3%)	11(25.0%)	0.715
Complications	Renal failure	12(100.0%)	33(75.0%)	0.097+
	Hepatic dysfunction	4(33.3%)	16(36.4%)	1.000
	Respiratory dysfunction	9(75.0%)	9(20.5%)	0.001**
	DIC	7(58.3%)	7(15.9%)	0.006**
	Shock	7(58.3%)	1(2.3%)	<0.001**
Number of organs dysfunction	Two organs dysfunction	4(33.3%)	13(29.5%)	1.000
	Three organs dysfunctions	2(16.7%)	9(20.5%)	1.000
	Four organs dysfunctions	6(50.0%)	0	<0.001**

DISCUSSION:

In the present study we found that the risk factors for poor outcome are source of infection in pancreatico biliary tract, higher APACHE II score, presence of organ dysfunctions like respiratory dysfunction, DIC, shock, presence of four or more than four organ dysfunctions. The variables like poor sensorium, metabolic acidosis were observed significantly in no survivors. The variables like age, gender, type of infection whether community acquired/ nosocomial, the type of organism whether E.coli/ K.pneumoniae, isolation of organism from urinary tract, unknown source of organism, presence of organ dysfunctions such as renal and hepatic are associated with poor outcome significantly. The independent predictors of mortality are APACHE II score>25, presence of complications like respiratory dysfunction, DIC, septic shock and presence of more than four organ dysfunction. In a study by KANG *et al.;* [3], the independent risk factors for mortality in bloodstream infections due to ESBL E.coli were neutropenia, peritonitis, septic shock, higher APACHE II score .Patients with peritonitis had higher mortality and most of the patients with peritonitis had advanced liver cirrhosis with spontaneous bacterial peritonitis. Though chronic liver disease was observed in 5 patients, it was not significantly associated with poor outcome when compared to survival group and none of the patients had peritonitis. Even in a study by TUMBERELLO *et al.;* [4], (Table-5) presence of liver disease was significantly associated with 21 day mortality. There was low mortality associated with pancreatico biliary tract infection in a study by KANG *et al.;* [3], the low mortality in that study was due to early intervention. In the present study two patients had pancreatico biliary duct infection and both of them expired. In a study by TUMBERELLO *et al.;* [4], risk factors associated with mortality rates were liver disease, previous hospitalization, high APACHE III score, presentation with septic shock, unknown source of blood stream

infection, inadequate initial antimicrobial treatment, multidrug resistant ESBLs.

Table-5: Comparision of Variables with Outcome in Different Study:

Parameter	Tumbrels *et al.;* [4], 2007			Present study,2008-2010		
	A N=71(%)	B N=115(%)	P value	A* N=12(%)	B** N=44(%)	P value
Mean Age in years ±SD	55± 20	54±19	0.83	53.83±16	48.41±14	0.258
Male sex	38 (53.5)	69 (60)	0.38	6(50.0)	19(43.2)	0.750
CRF	21 (29.6)	32 (27.8)	0.79	4(33.3)	8(18.2)	0.263
Nosocomial	65 (91.5)	31 ± 12	0.65	1(8.3)	5(11.4)	1.000
Diabetes	20 (28.2)	30 (26.1)	0.75	5(41.7)	26(59.1)	.338
Liver disease	15 (21.1)	11 (9)	0.02	2(16.7)	3(6.8)	0.289
Neutropenia	6 (8.4)	16(13.9)	0.39	0(0)	03(6.8)	1.000
Hematological malignancy	12(16.9)	33 (28.7)	0.06	0(0)	2(4.5%)	1.000
Solid tumor	20 (28.1)	32 (27.8)	0.02	1(8.3)	2(4.5)	0.522
Presentation with shock	8 (11.3)		0.005	7(58.3)	1(2.3)	<0.001
Organism isolated						
E.coli	33 (46.5)	71 (61.7)	0.04	11(91.7)	40(90)	1.000
K.pneumoniae	28 (39.4)	30 (26.1)	0.05	1(8.3)	4(9.1)	1.000
Site of infection						
Unknown	45 (63.4)	41 (35.6)	<0.001	4(33.3)	10(22.7)	0.470
Mean hospital stay	27±15	26±6	0.97	11.67±10.78	15.52±7.70	0.169
APACHE II score	36 ± 18	31 ± 12	0.03	27.75±8.06	19.32±6.04	<0.001

*A-non-survivors, **B-survivors

Carbapenems are the drugs with highest sensitivity (100%). This pattern is similar to other studies by JESUS *et al.;* , TUMBERELLO *et al.;* [4] (Table-6). After Carbapenems, Amikacin has highest sensitivity (75.9%), followed by Piperacillin/Tazobactam (70.7%), Cotrimoxazole (32.8%), and Gentamicin (25.9%). Among all the aminoglycosides Amikacin has highest sensitivity followed by Gentamicin, Tobramycin and Netilmicin. Quinolones are the drugs with least sensitivity accounting to 0% except in one case in which Levofloxacin was sensitive. Even in other studies by TUMBERELLO *et al.;* [4] & JESUS *et al.;* [5] Quinolones are the drugs with least sensitivity. However sensitivity is not 0% unlike in the present study. Other Beta-lactamase inhibitors like Ticarcillin /clavulanic acid is sensitive in 10.3% of cases. In this study Amikacin is more sensitive compared to Piperacillin/Tazobactam where as in studies by TUMBERELLO *et al.;* [4] & JESUS *et al.;* [5] Piperacillin/Tazobactam has more sensitivity compared to Amikacin.

Table-6: comparison of sensitivity pattern of antibiotics with different studies

Antimicrobial agent	TUMBERELLO *et al.;* [4] %	JESUS *et al.;* [5] %	PRESENT STUDY %
Carbapenems	100	100	100
Piperacillin/Tazobactam	84.5	93	70.7
Ticarcillin/clavulanic acid	-	16	10.3
Amikacin	100	85	75.9
Gentamicin	66.7	85	25.9
Tobramycin	-	80	12.1
Cefepime	-	37	0
Ciprofloxacin	7.8	36	0
Levofloxacin	7.8	-	1.7
Ofloxacin	-	-	0
Cotrimoxazole	41.1	37	32.8

CONCLUSIONS:

Poor sensorium, presence of septic shock, metabolic acidosis, organ dysfunction and APACHE II score > 25 is associated with poor outcome. Community acquired infection (87.9%), outnumbered nosocomial infection (12.1%). Most common source of sepsis was from urinary tract (67.2%) and source of sepsis from pancreatico biliary duct is associated significantly with

no survivors. No predisposing factor was significantly associated with poor outcome. Carbapenems are the drugs with highest sensitivity (100%) followed by Amikacin, Piperacillin/tazobactam. Quinolones are the drugs with least sensitivity almost accounting to 0%.

LIMITATIONS:

Main limitation of the study is sample size. Organ dysfunctions can occur in other septicemias also, so we cannot attribute ESBL organisms solely responsible for the organ dysfunctions as there are number of non-ESBL cases.. In predisposition factors for septicemia, the degree of predisposition was not considered (e.g. the degree of immunosupression, control of blood sugar in type 2 diabetes)

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