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Hospital Acquired Bloodstream Infection by Multi Drug Resistant Organisms-Alarming and Challenging Issue in the Intensive Care Units at Present Era

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Abstract

Hospital-acquired bloodstream infections (BSIs) cause high mortality in the intensive care units (ICUs) compared to wards. Furthermore, the isolation of multidrug resistant (MDR) organisms in ICUs add to the gravity of the condition making the treatment a bigger challenge. The present study was aimed to evaluate the prevalence, spread, and the possible MDR organisms contributing to ICU-acquired BSI & the source of the secondary BSI in the ICUs. A prospective study was conducted in four ICU of tertiary teaching hospital over a period of six months. Patient that developed features of BSI within 48 hours after hospital admission were included in the present study Blood culture was performed by an automated BacT/ALERT®3D system. The source of secondary BSI was identified by analysing culture results for the samples other than blood. These samples were taken within 48 hours of the patient's blood culture test being positive. A total of 50 patients (25%) had an ICU acquired bloodstream infection. Out of 50 patients, 74% of them had bacterial etiology. Thirty one patients (62%) among them developed multidrug resistant bacteraemia. Fifty six percent of Gram negative bacilli were multi drug resistant. The resistance to carbapenem was 42%. The most common MDR Gram negative isolate was identified as *Klebsiella pneumoniae* (n=12; 38.7%,) and the most common source was pulmonary infection (26.7% (n=12). 42% of isolates in our study were carbapenem resistant suggesting the need for a proper antibiotic policy in the ICUs. Prolonged stay in the ICU with mechanical ventilation was the critical risk factor and ICU mortality was high (38%).

Keywords: Intensive care unit, bacteremia, multidrug resistant, pulmonary infection

INTRODUCTION

Patients in intensive care units (ICUs) are at greater risk of developing nosocomial infections[1]. This problem is more in developing countries, largely due to lack of strict adoption of efficient infection control practices. The rate of nosocomial infections among ICU-admitted patients ranges from 11-60%[2]. Bloodstream infections (BSIs) represent a major class of hospital acquired infection prevalent in ICU patients. It claims for approximately 20% of the ICU-acquired cases and affects 5% to 7% of hospital admissions[3]. The fatality rate can range from 35-50% further adding to the complexity[4]. It may present itself as primary BSI or a secondary BSI from an already existing source of infection in the patient[5]. BSIs acquired in the ICUs are due to drug-resistant hospital strains like *Acinetobacter baumanii, K. pneumoniae, P. aeruginosa, S. aureus* etc. These MDR pathogens increase the mortality rate, length of stay in the ICU, and generate substantial extra costs[6]. It is necessary to know the risk factors, etiological agents, and source of secondary BSIs in the ICUs. These data can vary between institutions and ICUs within the hospitals. Hence each center should make its own therapeutic choice based on local surveillance data. Due to the lack of information in this area in the current study population, the study is being conducted to know the etiological agents of ICU acquired BSIs, their antibiotic susceptibility pattern, and the source of the pathogen to guide appropriate antimicrobial treatment.

METHODS

Study design & Population

Prospective cross-sectional study was conducted in four ICUs under the control of a 2062-bedded tertiary-care teaching hospital of Karnataka. The study was conducted for six month duration from January to June 2018.

Adult patients who developed features of BSI 48 hours after admission to the ICUs were included. All patients with ICU admissions of <=48 hours and with existing BSI shifted from the ward or other hospital to the ICU were not included in the study.

Total of 200 patients' blood was sent for culture and antimicrobial susceptibility testing during this study period from four different ICUs after clinical suspicion of bacteremia. Among 200 patients, 97 of them fulfilled the inclusion criteria and were analysed further.

Definitions

Nosocomial infection was defined as an infection that occurred 48 hours after the patient's admission[7].

ICU acquired BSI was defined as the patient having first positive blood culture two days after ICU admission without a prior positive blood culture with the same pathogen for at least 30 days.

A multidrug-resistant (MDR) micro-organism has been defined as an isolate with resistance to at least one agent in three or more antimicrobial categories. Extensively drug-resistant (XDR) microorganisms were defined as the organisms which exhibit susceptibility to only one or two antimicrobial categories[8].

Secondary BSI was defined by the isolation of the same strain of microorganism from blood culture and a suspected source[9]. In the absence of a known source, ICU-BSI was defined as primary.

Microbiology

About 8-10 ml of blood was collected from the patients and then directly inoculated in the labeled BacT/ALERT® FA Plus media (bioMerieux, Inc, Durham, NC). The bottles were then sent to the microbiology laboratory to process in the BacT/ALERT®3D system (bioMerieux, Inc, Durham, NC). This system works on the colorimetric principle. Specialized Liquid Emulsion Sensors (LES) at the bottom of each culture bottle visibly changes color from white to yellow when the pH changes due to the rise in CO_2 as microorganisms produce it. BACT/ALERT®3D instruments measure color changes. Positive flagged bottles contain microorganisms that were processed on 5% sheep blood and MacConkey agar and incubated at 37°C overnight. Simultaneously, Gram staining was performed directly from the bottle. The growth of microorganisms was identified by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) VITEK®MS, and antimicrobial susceptibility testing for the isolates was done by VITEK®2 system (BioMerieux, Inc, Durham, NC).

Data Collection and Analysis

Data regarding patient demographics, admitting specialty, duration of stay in the

ICU, presence of an underlying disease, details about antimicrobial therapy, and other relevant information was collected after taking the patient consent. The use of invasive devices and the number of days of their usage were also noted.

Culture results from other site-specific infections like lung infection, skin and soft tissue infection, urinary tract infection, intra-abdominal infection,, etc. were analysed within 48 hours of the positive blood culture to find out the source of secondary BSI. All positive blood cultures were then reviewed with reference to clinical records, imaging, and other laboratory data.

Statistical analysis

All the variables were presented as mean ± standard deviation, median and interquartile range, frequency, and percentage as deemed appropriate. Univariate logistic regression analysis was done to determine the risk factors for acquiring bloodstream infection. Further, multivariate logistic regression analysis was carried out using the 'Forward Wald" method to ascertain the independent predictors of acquiring BSI. All tests of significance were two sided with p-value < 0.05 having statistical significance. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 23.0 (Chicago, IL, U.S.A.) Unpaired t-test and Fischer's exact tests were used wherever applicable.

RESULTS

Patient demographics

A total of 1536 patients were admitted to the ICUs during the six months. Out of the 200 patients surveyed, 97 patients developed 106 nosocomial bacteremia episodes (88 patients with one episode and 9 patients with two episodes). Of these 97 patients, 50 (51.55%) had an ICU-acquired bloodstream infection, and the rest 47 patients (49.45%) were diagnosed to have a non-

Table 1. Effect of patients related characteristics on the susceptibility of acquiring BSI

Variables	ICU-Acquired BSI N=50 (51.55%)	Non-ICU Acquired BSI N= 47 (49.45%)	p Value
Age (Mean ± SD , Range)	52.14 ± 15.46 (20-79)	54.96 ± 16.68 (54-96)	0.386#
Male	35(70)	31(66)	
Female	15(30)	16 (34)	
ICU stay in days (Mean ± SD)	12.78 ± 11.307	7.85 ± 5.992	0.010#
Hospital stay in days (Mean ± SD)	19.36 ± 15.379	12.09 ± 9.261	0.007#
Underlying Co-morbid conditions ^:			
Diabetes	19(38)	12(27.7)	0.281
Chronic Renal disease	24(48)	18(38.8)	0.336
Cardiovascular disease	12(24)	4(8.5)	0.048
Chronic liver disease	15(30)	14(29.8)	0.982
Chronic lung disease	19(38)	13(27.7)	0.281
Malignancy	4(8)	5(10.6)	0.655
Neutropenia	5(10)	2(4.3)	0.288
Exposure to invasive devices			
Mechanical Ventilation No. of patients n (%)	36 (72)	22(46.8)	0.035^
Duration of exposure (Mean± SD)	8.12 ± 5.36	4.97 ± 3.76	0.024#
Urinary Catheter No. of patients	26(52)	14(29.8)	0.091^
Duration of exposure (Mean± SD)	10.00 ± 6.90	6.60 ± 5.41	0.549#
Central venous catheter(CVC) No. of patients	11(22)	3(6.4)	0.122^
Duration of exposure (Mean± SD)	10.44 ± 6.62	5.29 ± 4.68	0.227#

#: Unpaired t-test^: Fischer's exact test

ICU acquired bloodstream infection. The incidence was 32.6 per 1000 admissions.

The mean (SD) age of the patients with ICU-acquired BSI was 52.14 years (±15.46) and 70% were male. The mean (SD) ICU stay was 12.78 (±11.31 SD) days. (Table-1)

Concomitant conditions and risk factors for bloodstream infection

The common underlying co-morbid conditions in patients with an ICU-acquired BSI were renal disease (48%), diabetes (38%), and pulmonary disease (38%). There was also the presence of cardiovascular disease in 12 patients (24%). (Table 1).

The results of exposure to invasive devices are shown in Table 1. About 72% of patients were on mechanical ventilation during this course of ICU stay. The mean duration of a person being on mechanical ventilation was 8.12 days. Only 22% of the patients were exposed to a central catheter with a mean duration of 10.44 days.

Microbiological profile of the ICU-BSI

In patients with an ICU- BSI, 74% were bacterial. Gram-negative bacteria (GNB) were the predominant organism isolated (66.0% *(n= 33)*) followed by Gram-positive cocci and fungi (26%

Table 2. Microbial profile of BSI

Organisms Isolated	ICU Acquired BSI N (%)N=50	Non ICU Acquired BSI N (%)N=47
Gram Positive Bacteria	4 (8)	18 (38.3)
Staphylococcus aureus	1(2)	15(31.9)
Enterococcus faecalis	1(2)	1 (2.1)
Enterococcus faecium	2(4)	2(4.3)
Gram Negative Bacteria	33 (66)	28 (59.6)
Escherichia coli	9(18)	14(29.8)
Klebsiella pneumoniae	15(30)	6(12.8)
Enterobacter spp.	2(4)	3(6.4)
Serratia marcescens	1(2)	-
Pseudomonas aeruginosa	2(4)	2(4.3)
Acinetobacter baumanni	4(10)	3(6.4)
Yeasts	13 (26)	1(2.1)

Table 3. Antimicrobial susceptibility pattern of Gram-negative pathogens isolated from BSI

Antimicrobial drugs	*K. pneumoniae* N (%) (N=15)	*E. coli* N (%) (N=9)	*A. baumannii* N (%) (N=4)	*Enterobacter* N (%) (N=2)	*P. aerugonisa* N (%) (N=2)
Amikacin	9/15(60)	3/9(33.3)	-	0/2(0)	2/2(100)
Gentamicin	8/15(53.3)	7/9(77.8)	3/4(75)	0/2(0)	2/2(100)
Ampicillin	15/15(100)	9/9(100)	-	2/2 (100)	-
Amoxicillin-Clavulinic Acid	12/15(80)	7/9(77.8)	-	2/2(100)	-
Cefuroxime	14/15(93.3)	9/9(100)	-	2/2(100)	-
Cefotaxime	14/15(93.3)	9/9(100)	-	2/2(100)	-
Ceftazidime	-	-	4/4(100)	-	2/2(100)
Ciprofloxacin	12/15(80)	7/9(77.8)	4/4(100)	1/2(50)	2/2(100)
Trimethoprim Sulphamethoxazole	12/15(80)	9/9(100)	4/4(100)	2/2(100)	1/2(50)
Cefepime	11/15(73.3)	7/9(77.8)	4/4(100)	1/2(50)	2/2(100)
Cefoperazone-sulbactam	11/15(73.3)	4/9(44.4)	3/4(75)	0/2(0)	2/2(100)
Imipenem	11/15(73.3)	4/9(44.4)	4/4(100)	0/2(0)	2/2(100)
Piperacillin-tazobactam	13/15(92.3)	4/9(44.4)	4/4(100)	0/2(0)	2/2(100)

Table 4. Statistics of acquiring BSI from different sources of infection

Source	ICU- BSI	Non ICU- Aquired BSI
Pulmonary Infection	12(26.7)	2(9.52)
Urinary Tract Infection	6(13.3)	7(33.33)
Surgical Site Infection	2(4.4)	2(9.52)
Digestive Tract Infection	10(22.2)	2(9.52)
Skin/Soft Tissue Infection	1(2.2)	0(0.00)

(n= 13)). Amongst the GNB, the most frequent organism isolated was *Klebsiella* spp. (30% *(n=15)*) followed by *Escherichia coli* (18% *(n=9)*) and *Acinetobacter* spp. (8% *(n=4)*). *Enterococcus* spp. was the major (6% *(n=3)*) isolates among Gram positive organisms. Among the fungi, *Candida albicans, C. tropicalis*, and *C. parapsilosis* were found in 8% *(n=4)* of the isolates.(Table 2).

Antibiotic susceptibility pattern

Total no. of MDR organisms isolated from BSI in the ICU was 62% (31/50). MDR Gram-negative pathogens dominated (90.3%, 28/31) in ICU BSI. Frequently isolated MDR Gram-negative organisms were *K. pneumoniae* (38.7%), *E. coli* (25.85%), and *A. baumanii* complex (16.1%). 91.7% *K. pneumoniae* (11/12) , 75% (3/4) *Acinetobacter baumanii* complex, and all *Pseudomonas* spp. were extensively drug resistant. 56% of (5/9) *E. coli* were XDR, and the remaining of them were ESBL producers. All the XDR strains were sensitive to colistin and aminoglycosides. ESBL producing GNBs were mostly sensitive to carbapenems (88.9% *(n=9)*) followed by piperacillin-tazobactam (85.7% *(n=7)*) and cefoperazone-sulbactam (81.8% *(n=9)*) (Table 3)

Among Gram-positive cocci, a single isolate of methicillin-resistant *Staphylococcus aureus* and two strains of *Enterococcus faecium* showing multi-drug resistance against penicillin, gentamycin, doxycycline, ciprofloxacin, and erythromycin.

Source of bloodstream infection

Out of 50 patients with ICU-acquired BSI, 38% had a primary bloodstream infection, and 62% of the BSI were secondary (Table 4). Amongst the secondary ICU- BSI, the most common source was pulmonary infection (26.7% (n=12)), followed by digestive tract infection (22.2% (n=10)).

DISCUSSION

The present study evaluated the etiological agents, antimicrobial susceptibility pattern, and source of secondary BSI acquired in intensive care of a tertiary care hospital. The incidence of ICU acquired BSI in our study was 6.4%. A multicentre study (EPIC II) in ICUs conducted by Vincent et al[10], showed that in ICU approximately 15% of patients had a BSI on the day of the study. Another study conducted by Sante et al. from 2009 to 2014 in a tertiary care hospital, documented 22% ICU associated BSI[11].

The mean age of our cohort with an ICU-acquired BSI was 52.14 years, and 70% was male. Our findings corroborate with a previous study in south India by Khan et al. which has also found that male patients at the age group of 40-50 years had more frequency of ICU-acquired BSI[12]. It may be due to the presence of underlying comorbid conditions like diabetes, chronic renal disease, liver disease, hypertension in this age group of male patients. These conditions also made them visit the hospital several times and consequently increase the chance of exposure to several invasive devices. Zhang et al. also mentioned exposure to invasive devices as an important risk factor for bacteremia acquisition in this age group[13].

Significant risk factors for ICU acquired BSIs are exposure to invasive devices, prolonged hospital stay, immunosuppression, etc[3]. Chronic renal disease (48%), diabetes (38%), chronic liver disease(30%) were the main underlying co-morbid diseases noted in this study. A large number of patients also had the requirement of invasive devices like mechanical ventilation (72%), urinary catheter (52%), and central venous catheter (22%). Aynur et al. analysed 65 patients with ICU-BSI and found chronic renal failure (CRF),diabetes mellitus (DM), mechanical ventilation and use of an arterial catheter, as significant risk factors[14].

The ICU stay of the patients was estimated to be about 12.78 ± 11.307 days, and prolonged hospital stay significantly (p=.007) attributed to the acquiring BSI in the ICUs. Adrie et al. analyzed 571 ICU–BSI occurring amongst 10,734 patients. They found a catheter-related infection, lung infection, and peritonitis were the major cause of secondary BSI[9]. In this study, ventilator associated pulmonary infection (26.7%) was the most common source followed by abdominal

infection (22.7%) All the VAP causing strain led to BSI in the ICU were carbapenem resistant. Prolong ventilator days (8.12 ± 5.36) was a significant risk factor (p=.024) of this. Hatem et al.[15] documented the ICU-BSI secondary to ventilator-acquired pneumonia in 25% of cases. VAP was reported to cause secondary bacteremia in 15-21% cases in another study[3]. Prolonged ventilation damage the host defense system particularly mucocilliary mechanism and helps the bacteria to invade the bloodstream.

In this study,Gram-negative bacteria predominated (66%), which is consistent with the previous research[5]. Commonly isolated GNBs were *Klebsiella pneumoniae, E. coli* and *Acinetobacter baumanni* complex,which is similar to other ICU studies in southern India[16,12]. *Klebsiella pneumoniae* and *Acinetobacter baumanni* were the common organisms isolated in VAP associated bacteremia. Sante et al. also documented a similar findings in their study[11]. *E.coli* and *Klebsiella* predominated in the abdominal infection that led to the secondary case of BSI. Here, ESBL-producing *Enterobacterales* was challenging for clinicians, due to the resistance of the organisms to third generation cephalosporin. As consequence meropenem was the first choice of treatment and this may be due to high carbapenem resistance seen among isolates.

The epidemiology of infections in our ICUs has been primarily centered on the MDR organisms (62%). High resistance to carbapenem (68%)- non-fermenter GNBs (100%) followed by *Klebsiella pneumoniae*(83%) associated with the mortality of 38%, which is similar to the study by Lijun Tian et al.[17] Such a high percentage of MDR, especially carbapenem resistant, maybe due to inappropriate usage of antibiotics in the wrong dosage, failure of antimicrobial de-escalation, longer usage of broad spectrum antibiotics. This strongly suggests that meticulous infection control in ICUs may reduce ICU-related mortality in critically ill patients.

There were a few limitations to our study. Our study included only a few ICUs for a short period, which cannot be generalised for all types of ICUs globally or nationally. Detailed antimicrobial therapy data not included in this study which could have answered the high rate of MDR.

CONCLUSION

The present study was conducted in four medical ICUs of, a tertiary care teaching hospital of south Karnataka to guide the physicians on the most suitable antimicrobial algorithm to be followed. Multidrug resistant GNBs were the predominant group of organisms causing BSI in the ICUs,especially *K. pneumoniae* and *A. baumannii*. They showed resistance even to carbapenem. This study thus will help in effective formulation of antibiotic policy while emphasizing on the need to follow stringent infection control practices especially in the ICU.

VAP was the common source for secondary BSI in intensive care. Prolonged ICU stay and multiple co-morbidities significantly attributed to the risk of acquiring bloodstream infection. This indicates towards special care while dealing with patients on ventilator or other such devices especially with older patiensts or patients with reported history of co-morbidities in order to decrease the risk of acquiring a BSI. Also, early detection of acquired BSI in high-risk patients in order to start early therapeutic treatment is required.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

BB was the guarantor of this research work and was involved in study design, literature search, and manuscript preparation; VKE & CM was involved in the concept of the study, bacteriological evaluation and manuscript editing and review; SM was responsible for collection of samples, data analysis, statistical analysis, and interpretation of data. MV was involved in clinical analysis, manuscript editing and language editing. This manuscript has been read and approved by all the authors.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

An approval was obtained from the institutional ethics committee prior to commencement of the study.

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