Prevalence of Septicaemia and Antibiogram of Different Etiological Agents in Patients of Intensive Care Units of a Tertiary Care Centre in Northern India

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Original Article

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Abstract

Background

Septicaemia is a leading cause of mortality in ICU patients. Any delay in diagnosis and /or antibiotic treatment have been shown to increase in mortality.We planned to study the prevalence, bacteriological profile of septicaemia along with their antibiogram in patients of different ICUs in a tertiary care Hospital, Northern region.

Materials and Methods

Blood culture was performed on total of 223 blood samples from 218 patients suspected for septicaemic episodes using Brain Heart Infusion (BHI) broth. The isolates were identified by standard microbiological techniques and their antibiotic susceptibility testing was performed by Kirby Bauer method.

Results

Bacterial growth was seen in 54 samples (54 episodes of septicaemia) from 49(22.47%) patients (40, 4, 5 from Neonatal ICU, Medicine ICU, Surgical ICU respectively). The commonest isolate was *Staphylococcus aureus* (45.45%) [80% in NICU, 12% in MICU & 8% in SICU], followed by *Klebsiella* (30.9%) [100% from NICU], and *Pseudomonas aeruginosa* (9.1%) [40% in NICU, 20% in MICU & 40% in SICU]. The Gram positive isolates showed high sensitivity against teicoplanin (96%), vancomycin (93%), netillin (76%), erythromycin (72%), & gentamicin (72%), The Gram negative isolates showed high sensitivity against imipenem & amikacin.

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Conclusion

As prevalence of septicaemia and its etiology varies among hospitals, a rational protocol is warranted to manage sepsis of critically ill patients based on adequate knowledge of sensitivity pattern of prevalent causative agents.

Keywords: Sepsis, ICU, *Klebsiella*, *Staphylococcus aureus*, sensitivity

Introduction

Bloodstream infection (BSI) is one of the prevalent infections among patients admitted to Intensive Care Units (ICUs) and the incidence is increasing with advance in medical technologies[1]. Sepsis causes significant morbidity and the mortality rate is estimated to vary from 25% to 80%[2, 3].

Septicaemia is a term to denote those clinical states in which bacteria are present in the bloodstream and cause systemic symptoms such as fever, tachypnea, delirium, thrombocytopenia, leukocytosis or leukopenia, lactic acidosis, disseminated intravascular coagulation (DIC), elevations in C-reactive protein, haptoglobin and hypotension. Septicaemia is an acute condition. It has a connotation of urgency; unless the right things are done quickly, the patient is likely to die[4].

Organisms of group Enterobacteriaceae continues to be a major cause of Gram negative aerobic bacillary bacteraemia. This increase in invasion by Gram negative bacilli is perhaps because the organisms translocate more efficiently from the gastro-intestinal tract than do other bacteria[5,6]. ICU associated infections are mostly due to *Staphylococcus aureus* & Coagulase negative *Staphylococcus epidermidis* arising from contaminated intra-vascular devices like artificial heart valves, intravenous and intra-arterial catheters[7].

Now it has become a common practice to institute early empirical therapy with broad-spectrum antibiotics in patients presenting with clinical features suggestive of septicaemia. Selection of appropriate antibiotics that can cover both positive and Gram negative micro organisms, at this phase is usually critical. This selection is depending on factors like epidemiological evidences, antibiotic resistance patterns and probable infective organisms[8]. Prevalence of micro organisms causing septicaemia in ICUs depends on environmental and geographical locations. In developing countries like India, many hospitals are not equipped with isolation facilities[9] and it is of high probability that prevalent microorganisms in hospitals of these countries may be different from those in developed countries. Apart from different prevalence, these micro-organisms show variable degree of resistance to antibiotics due to irrational use of antibiotics. This study aims to determine the prevalence of the bacterial agents causing septicaemia in three ICUs and to determine the antibiotic susceptibility pattern so as to help clinicians to adopt the appropriate antibacterial therapy. The epedimiological data on septicaemia would be helpful for the intensive care unit (ICU) physicians and scientific researchers, to understand the epidemiology of sepsis, and to evaluate the efficiency of therapeutic trials.

Material and Methods

Data collection:

The A total of 223 blood samples from patients having signs & symptoms of septicaemia like fever or hypothermia, leukocytosis (W.B.C >12000/mm^3) or leucopenia (<4000/mm^3), tachypnea (HR>90 beat/min), admitted in different ICUs.The data were collected and sent to the Department of Microbiology for culture and sensitivity. Datasuch as age, sex, I.C.U type, presenting symptoms, patient history were included.

Study Design and participants:

This is a cross-sectional study of one year (from 1stJanuary 2011 to 27thFebruary 2012). A total of 218 patients, aged newborn to 90 years. Most of the patients were from the "0 to 28 days" group. Out of 218 patients, 56.9% were males and 43.1% were females.

Sample size calculation:

The sample size was calculated using the formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n=sample size, Z = Z statistic for a level of confidence, P = expected prevalence and d=the precision.

From the existing data, the prevalence of septicaemia in ICU patients varied from 12-38.5%. However most of the studies available were done on a western population setting. Keeping this limitation in mind and assuming the prevalence to in between foresaid range. With a prevalence rate of 12% and a precision of 0.05, the sample size works out to be 163, but it works out to be 364, if the maximum quoted prevalence rate of 38.5% and a precision of 0.05 are to be used. However, in the 1-year period we performed an interim analysis and terminated the study with 218 patients.

Inclusion criteria:

During the study period, all the patients presenting to the different ICUs with signs and symptoms of sepsiswere enrolled.To be eligible patients must have all of the following:

- Must be admitted or transferred to an Intensive Care Unit.
- Have a high clinical suspicion of an infection
- Have sepsis as defined by an infection together with two or more SIRS criteria

Exclusion Criteria:

Patients with the following criteria will be excluded:

- Patients in whom the sepsis has been present before the beginning of the study period.

Statistical Analysis and Data Analysis:

Descriptive statistics were calculated using Microsoft Office Excel 2010. Percentages were used in this study to analyze the data.

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Ethics committee approval:
Institutional ethics committee approved this study. The purpose of the study was explained to patients or their parents and were ensured strict confidentiality. Written informed consents were taken from patients or parents in case of children prior to the study.

Methodology:
Blood samples for culture were collected before the commencement of antibiotic treatment following strict aseptic precautions. If empirical antibiotics were already started, the collection was timed before the next dose of antibiotic was due or half an hour before predicted peak of temperature with the next best time just as temperature starts to rise[10]. About 1 ml of blood was collected in case of neonates, 5 ml in case of children and around 10ml in case of adults[11] and were inoculated into blood culture bottles containing 10 ml (for neonates) & 50 ml (for small children and adults) Brain Heart Infusion (BHI) broth without switching needles to allow 1:5 – 1:10 dilutions.. The blood culture bottles were incubated at 37º C aerobically.
The blood culture bottles were examined daily to look for growth which can be observed as turbidity, haemolysis of red blood cells, gas bubbles in the medium, small aggregates of growth in broth or along the walls of the bottle.
After overnight incubation, the samples were subcultured onto 5% sheep blood agar, Mac Conkey agar & Chocolate agar. When there was no growth observed on the plates by the next day, subcultures were again repeated from the broth on day 3, day 4 and finally on day 7. Finally when there was no growth on 7th day then only the samples were reported as sterile and discarded.
The isolated bacteria were identified by colony morphology, Gram staining, catalase test, oxidase test, coagulase (tube), motility, and standard biochemical tests including oxidative-fermentative test, triple sugar iron, nitrate reduction test, indole production, methyl red test, VogesProskaeur test, citrate utilization test, urease production, carbohydrate degradation tests and amino acids decarboxylation tests.
AST was performed by Kirby Bauer disc diffusion method as per National Committee for Clinical Laboratory Standards (NCCLS)[12]. Mueller Hinton Agar plates (MHA) and commercially procured antibiotic discs (Himedia) were used. The discs used were amikacin (30 µg) [Ak], ciprofloxacin (5 &30 µg) [Cf], cotrimoxazole (1.25/23.75 µg) [Co], erythromycin (15 µg) [E] gentamicin (10 µg) [G], netillin (30 µg) [Nt], oxacillin (1 µg) [Ox], penicillin (10 µg) [P], tetracycline (30 µg) [T], vancomycin (30 µg) [Va], ampicillin (10µg) [A], amoxicillin/clavulonic acid (30µg) [Ac], ceftazidime (30µg) [Ca] cephotaxime (30µg) [Ce], imipenem (10µg) [I], Teicoplanin [Tei]

Result:

The blood samples were processed from 218 patients(56.9% male and 56.9% female) from different ICUs. The age group and the bacterial growth in samples from male and female patients are given in Table-1.

Table 1: The age group and sex of the patients admitted in ICUs.

Age group	Number of patients			Number of positive cases		
	Male	Female	Total	Male	Female	Total
0-28 d	101	74	175	24	16	40
28d-20y	6	9	15	4	0	4
21y-40y	11	9	20	2	2	4
41y-60y	4	1	5	1	0	1
>60y	2	1	3	0	0	0
Total	124 (56.9%)	94 (43.1%)	218 (100%)	31 (63.3%)	18 (36.7%)	49 (100%)

Out of 218 cases, 49 patients were culture positive (63.27% male and 36.73% female). The patient distribution from different ICUs was 80.3%, 15.1% and 4.6% from NICU, MICU and SICU respectively. The total positive culture patients were 22.9%, 12.1% and 50% from the NICU, MICU and SICU respectively (Table-2).

Table 2: Number of patients from different ICUs and the number of patients showing positive blood cultures.

ICUs	Culture and sensitivity			Blood culture positive		
	Male	Female	Total (%)	Male	Female	Total (%)
NICU	101	74	175(80.3)	24	16	40(22.9)
MICU	18	15	33(15.1)	2	2	4(12.1)
SICU	5	5	10(4.6)	5	0	5(50)
Total			218 (100)	31	18	49 (22.47)

NICU, Neonatal ICU; MICU, Medicinal ICU; SICU, Surgical ICU; C/S, Culture and sensitivity.

A total of 223 blood samplewere processed from a total of 218 patients and a total 54 episodes of septicaemia had been seen in ICU patients. 45 patients had single episode while 3 patients had double episode and only one patient had a triple episode of septicaemia (Table-3).

Out of 54 episodes of septicaemia, 53 were mono-microbial; while one was polymicrobial (2 isolates), so total 55 bacterial isolates. Most of the isolates were from the NICU, followed by SICU and MICU. Out of the 55 isolates, 26 (47.27%) were Gram-positive cocci and 29 (52.72%) were Gram-negative bacilli. *Staphylococcus aureus* was the most frequently isolated Gram-positive organism while *Klebsiellaspp*(30.9%) heads the list among the Gram-negative isolates in ICU patients. The etiological agents in different ICUs are listed in Table-4.

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Table 3: Number of episodes of septicaemia.

ICUs	Blood samples	Septicaemic episodes	Number of episodes in patients			
			Single Episode	Double Episode	Triple episode	Total
NICU	180 (80.7%)	45	36	3	1	45
MICU	33 (14.8%)	4	4	0	0	4
SICU	10 (4.5%)	5	5	0	0	5
Total	223	54	45	3	1	54 (24.21%)

NICU, Neonatal ICU; MICU, Medicinal ICU; SICU, Surgical ICU.

Table 4: Bacterial isolates from different ICUs in order of frequency.

	Sa* (%)	Kleb (%)	Pseu (%)	Entero (%)	Acein (%)	Citro (%)	E.coli (%)	NEc (%)	CoNS* (%)	TOTAL (%)
NICU	20	17	2	1	2	1	1	1	1	46(83.6)
MICU	3	0	1	0	0	0	0	0	0	4(7.2)
SICU	2	0	2	1	0	0	0	0	0	5(9.1)
TOTAL	25 (45.4)	17 (30.9)	5 (9.1)	2 (3.6)	2 (3.6)	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)	55(100)

Sa,Staphylococcusaureus;Kleb,Klebsiellaspecies;Pseu, Pseudomonas eruginosa;Entero,Enterobacterspecies;Acein, Acinetobacterspecies;Citro,Citrobacterspecies;E.coli,Escherihiacoli;NEc, Non lactose fermenting Escherichia coli;CoNS, Coagulase negative Staphylococcus;NICU, Neonatal ICU; MICU, Medicinal ICU; SICU, Surgical ICU.

- 53 cases were monomicrobial while 1case was polymicrobial (2 isolates)

* Gram positive isolates

Table 5: Sensitivity pattern in percentage (%) of Gram positive isolates.

Organism	Ak	Cf	CO	E	G	Nt	Ox	P	T	Va	Tei
S. aureus	64	32	28	72	72	76	40	16	50	93	97
CoNS	100	NT	NT	100	0	NT	100	0	100 (IS)	100	NT

Ak, Amikacin; Cf, Ciprofloxacin; Co, Cotrimoxazole; E, Erythromycin; G, Gentamycin; Nt, Netilin; Ox, Oxalcillin; P, Penicillin; T, Tetracyclin; Va, Vancomycin; IS, intermediate sensitive; NT, Not tested; *S.* aureus, Staphylococcus aureus; CoNS, Coagulase negative Staphylococcus.

Table 6: Sensitivity pattern in percentage (%) of Gram negative isolates.

Organism	Ak	A	Ac	Ca	Ce	Co	Cf	G	I
Klebsiella	58.8	0	0	11.75	11.75	35.3	23.5	0	88.2
Pseudomonas	80	NT	NT	100	60	5	60	80	60
Citrobacter	0	NT	NT	0	0	100	0	0	100
Acinetobacter	100	50(IS)	NT	50	100	100	100	50	NT
Enterobacter	100	50	NT	50	50	NT	100	50(IS)	100
NEc	100	NT	NT	0	0	100	0	0	100
E.coli	100	NT	NT	0	0	100	0	0	100

Ak, Amikacin; A, Ampicillin; Ac, Amoxicillin/Clavulonic acid; Ca, Ceftazidime; Ce, Cephotaxime; Co, Cotrimoxazole; Cf, Ciprofloxacin; G, Gentamycin; I, Imipenem; IS, Intermediate sensitive; NT, Not tested; NEc, Non lactose fermenting Escherichia coli; E.coli, Escherichia coli.

The antibiotic susceptibility testing (AST) of the Gram-positive and Gram-negative isolates were tabulated in Table-5 and Table-6 respectively.

Discussion:

Septicaemic prevalence:

The prevalence of septicaemia varies with considerable fluctuation over time and place which indicate that there is a need for continuous monitoring of causative organisms and their drug susceptibility pattern at a local level. In our study, the prevalence of septicaemia was 22.47% (Table-2), which is comparable to the results of previous studies[13,14,15]. Though, a low prevalence of 18.2% and 12% was reported in the study of Turkish university hospital and European ICUs respectively[16,17] whereas the Iranian ICUs study has reported a high prevalence rate (38.5%) of septicaemia[18]. The high variability in the prevalence rate could be due to differences in sticking to aseptic techniques from one hospital to another. The practices like hand washing, sterilization and disinfection of equipment and devices, aseptic precautions during invasive procedures and staff education play an important role in the prevalence of septicaemia especially in ICUs.

Blood culture positivity:

In the present study, 24.21% cases had positive blood culture (Table-3). Various authors have reported blood culture positivity in the range of 7.89-56% [19, 20, 21]. A low blood culture isolation rate in some studies might be due to several reasons, e.g. Administration of antibiotics before blood collection, so the timing of blood collection for culture should be judiciously done or the possibility of infection with anaerobes. A study has reported that 26% of all the septicaemia was caused by anaerobes [22].

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Is gender and age a risk factors in sepsis?

In the present study, positive cultures were reported in 63.3% males and 36.7% females (Table-1); similar observations were reported in a previous study [23]. Previous studies also suggested that male gender increases the risk for developing sepsis. They demonstrated the immunosuppressive effects of male sex hormones and immune enhancing effects of female sex hormones in the context of depression of immune function after trauma and haemorrhage in males[23, 24].

The ages of patients ranged from newborn to 90 years. The numbers of positive blood cultures from NICU, SICU and MICU were 22.9%, 50% and 12.1%respectively (Table-2). Whereas the highest positive rate was in NICU (81.63%), it could be attributed to lower immunity in neonates. This is further supported by previous studies that pointed out a high rate of positive cultures (47.5% and 24.88%) in neonates [25, 26]. Exposure to life-saving invasive procedures, severity of sickness and the potential for patient-to patient transmission common risk factors for all ICU's patients.

Etiological agents:

The analysis of microbiological characteristics of septicaemia in this study showed that Gram-negative bacteria were the most common pathogens in septicaemia (52.72%) which was quite different from the report that Gram-positive bacteria were predominant in previous studies[27,28]. However results in this study were consistent with some of previous studies[29, 30, 31]. The reasons for the changes in the microbiological patterns of septicaemia in this study is probably a result of complex interactions involving patient's underlying conditions, the demographic and geographic factors, the extensive use of extended-spectrum antibiotics, less attention to sanitary precautions, the invasive interventions, and the quality of care provided.

The *Staphylococcus aureus* (45.45%) is the commonest pathogen among the Gram-positive isolates (80%, 12%, and 8% from the NICU, MICU and SICU respectively) which may be due to increased use of invasive procedures.

A study among paediatric ICU patients reported that pharyngeal *S. aureus* carriage (92.6%) was more common than nasal carriage; it also exceeds the carriage rates in adults (58 to 84%). These pharyngeal / nasal *S. aureus* carriage is a well-known risk factor for infection[32].

The Gram-negative septicaemias in ICUs frequently originate from respiratory or gastrointestinal route, thus the common isolates being *Klebsiella, Pseudomonas* and *Enterobacter*species. This is confirmed by our study as amongst the Gram-negative isolates *Klebsiella* species (30.9%) [100% from NICU], *Pseudomonas aeruginosa* (9.1%) [40%, 20%, 40% from the NICU, MICU and SICU respectively], *Enterobacter* species (3.6%) [50% from NICU and 50% SICU)], *Acinetobacter* species 3.6 [100 % from NICU] tops the list, while the other isolates were *Escherichia coli*, Non Lactose fermenter *Escherichia coli* and *Citrobacter* Prevalence of septicaemia and antibiogram in patients of ICUs species [1.8% each from NICU]. These findings further in line with some previous studies[30, 32, 33].

Antibiotic sensitivity profile:

The AST showed that *Staphylococcus aureus* were highly sensitive to Teicoplanin & vancomycin while they were highly resistant to penicillin 84%, cotrimoxazole (72%), and ciprofloxacin (68%) as those drugs are commonly used by the practitioners. A similar high rate of Penicillin resistance was seen in *S. aureus*(95.9%) in a study conducted in Lucknow[25]. Forty percent of strains were methicillin resistant *Staphylococcus aureus* (MRSA).

Klebsiella species showed good sensitivity against imipenem and amikacin while in case of *Pseudomonas aeruginosa* effective drugs were Ceftazidime, amikacin and gentamicin. None of the strains of *Klebsiella*were sensitive to ampicillin and amoxyclav, similar 100% resistance was reported in a previous study[25]. Multiple drug resistance was also seen among Gram-negative isolates.

Conclusion:

Staphylococcus aureus and *Klebsiella* species are the common isolates causing septicaemia in ICU patients. Our study suggests that the use of broad spectrum antibiotic should cover these pathogens. The findings warrant that the life threatening complications of septicaemia can be prevented by isolation of the causative agent if possible and judicious use of preventive as well as therapeutic antibiotics.

Limitation of the study:

We have not done anaerobic blood culture. Use of automated blood culture techniques could have refined the results. The multiple episodes of septicaemia in a patient (n=4) have been included in the number of specimen which might affect the blood culture positivity rate.

Further scope of study:

The common risk factors like respiratory distress, prematurity, surgery, trauma and invasive procedures in different ICUs that predispose septicaemia could be considered in future studies. The inclusion of 2 viral and fungal agents would enhance the adoption of proper treatment policies.

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Authors' contributions:

All authors contributed equally in this study in various fields such as study design, acquisition of data, revision and preparation of the manuscript. All authors have gone through the manuscript and finalize the same for publication.

Conflict of interest:

There is no conflict of interest among authors arising from the study.

What this study adds:

The prevalence and etiological agents of septicaemia varies among hospitals thus such studies should be done at regular time interval to develop a rational protocol to manage morbidity of ICU patients.

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