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Original Article

Predictors of mortality in adult sepsis.

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ABSTRACT

Aims: The aim of this study was to identify clinical, laboratory and microbiologic features that may be predictive of mortality in sepsis and help achieve an early stratification to identify those at high risk of death in adult patients. Methods: A total of 298 adult patients with clinical diagnosis of septicaemia were studied. Patients with positive blood culture were included in the study. Other specimens included sputum, urine, pleural fluid, stool, ascitic fluid, burn and surgical wound swabs, throat swabs, intravenous catheter tips and endotracheal tips to identify the source of infections. All samples were processed using standard microbiological techniques Results: Blood culture was positive in 100 patients (33.55%). Gram-negative organisms (70.47%) were more common than gram-positive organisms (29.53%). The overall mortality from bacteraemia was 18%. Bacteraemia associated mortality notable after the age of 45. The mortality rate in polymicrobial septicaemia was 3 out of 5 (60%), which was higher than monomicrobial septicaemia (15.78%). Factors potentially related to the outcome of bacteraemia were nosocomial acquisitions, age >45 years, bacteraemia caused by some difficult to treat organisms, such as Pseudomonas spp. and polymicrobial bacteraemia. The incidence of primary blood stream infection was seen in 25 cases and secondary blood stream infection was seen in 75 cases. The most common source of bacteraemia was gastrointestinal tract (27) followed by respiratory tract (22), wound (11), urinary tract (10) and Intra venous(I.V.) catheters (5). The common predisposing factors were recent surgery, Diabetes, cancer, burns, HIV, cirrhosis and neutropenia. Mortality among patients with hospital acquired bacteraemia was more than community acquired bacteraemia. Conclusion: Awareness of the risk factors, clinical signs and symptoms, pathophysiology, and updates in the management of sepsis can enhance the nursing care for patients with severe sepsis to promote best practices for sepsis care in the intensive care unit.

1. Introduction

Sepsis refers to the systemic response to serious infection [1]. Any site of infection can result in sepsis or septic shock. Blood cultures yield bacteria or fungi in approx. 20-40% of cases of severe sepsis, and 40-70% of cases of septic shock. The presence of bacteraemia is an indicator of disseminated infection, and also generally indicates a poorer prognosis when associated with localized disease [2]. Sepsis has been reported to be the most common cause of death in non-coronary intensive care units. It is an increasingly common cause of mortality and morbidity particularly in elderly, immunocompromised and critically ill patients. Approximately 25-35% of patient with severe sepsis and 40 to 55% of patients with septic shock die within 30 days [2]. The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference was held in 1991 with the goal of agreeing on a set of definitions that could be applied to patients with sepsis and its sequelae. The aim of this study was to identify clinical, laboratory and microbiologic features that may be predictive of mortality in sepsis and help achieve an early stratification to identify those at high risk of death.

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2. Materials and Methods

Two hundred and ninety eight adult patients (>18years) with suspected sepsis were chosen.

Sepsis was defined as SIRS (systemic inflammatory response syndrome) with suspected or

proven microbial etiology. SIRS includes the presence of at least two of the following:

1. Oral temperature of >38^{0}C or <36^{0}C,
2. Respiratory rate >24/min or PaCO2 <32 torr,
3. Heart rate > 90/min,
4. Leukocyte count >12,000/l or <4000/l or >10% band forms [2].

Patients with positive blood culture were included in the study. Blood was collected using sterile aseptic precautions for aerobic culture and sensitivity (2 samples of 10 ml each for routine aerobic culture and 3 samples of 10 ml each for Infective endocarditis) and routine investigations. Blood was obtained immediately once the sepsis was suspected or within 24hrs of admission to the hospital, before starting treatment [3]. Other specimens included sputum, urine, pleural fluid, stool, ascitic fluid, burn and surgical wound swabs, throat swabs, intravenous catheter tips and endotracheal tips to identify the source of infections. All samples were processed using standard microbiological techniques. Any growth was identified and antibiotic sensitivity was done [4]. Probable contaminants were excluded.

The following definitions were considered for interpretation of results:

A. Bacteraemic episode:

A bacteraemic episode was defined as isolation of one or more organisms from the same patient on one or more occasions when clinical evidence suggested a common source and these isolations were not separated by an asymptomatic period during which no antibiotics were given. When the source was unknown or multiple sources were evident, all blood cultures that were positive within 48 hours of another positive blood culture were considered to represent one bacteraemic episode [5].

B. risk factors:

1. Chemotherapy: Cytotoxic antineoplastic agents given within 6 weeks prior to the positive blood culture.
2. Steroids: More than one dose of oral or parenteral corticosteroid given within 2 weeks prior to the positive blood culture.
3. Intravenous catheters: The presence of central venous catheter, arterial catheters or hemodialysis shunts at the time the culture was positive.
4. HIV Infection: Seropositivity for human immunodeficiency virus.
5. Diabetes: Either insulin dependent or non-insulin dependent diabetes mellitus [6].

C. Primary blood stream infection: There was no documented distal source. The infection was either a laboratory confirmed bloodstream infection or clinical sepsis [7].

D. Secondary blood stream infection: An infection that develops subsequent to a documented infection with the same microorganism at another body site [7].

E. Hospital acquired infections: Bacteraemia was considered to be hospital acquired if blood cultures performed 48hrs after admission were positive and no clinical evidence of infection (fever, leukocytosis, or other signs or symptoms) was present on admission [6].

F. Community acquired Infection: If blood cultures performed within 48hrs of admission were positive and the patient had not been hospitalised during the previous one month [6].

G. Death: Death was attributed to an organism infection if one or more of the following criteria were fulfilled (and there was no other explanation for death)-

A blood culture positive for that organism at the time of death; persistent focus of organism infection at death; persistent signs or symptoms of infection such as fever, leukocytosis or hypotension; or the occurrence of death for which there was no other explanation, within the first 7 days after documentation of organism bacteraemia [8].

3. Results

A total of 298 adult patients with clinical diagnosis of septicaemia were studied. Blood culture was positive in 100 patients (33.55%). Gram-negative organisms (70.47%) were more common than gram-positive organisms (29.53%). The commonest organisms isolated were Salmonella Spp. (17) fallowed by Pseudomonas aeruginosa (16) and Klebsiella pneumoniae (11%) (Table 1). It was interesting to note that Acinetobacter spp. was a significant cause of bacteraemia (10%). Among 100 septicaemia patients studied, 60 were male (60%) and 40 were female (40%) (Table. 2). The patients age ranged from 18 to 88 years (mean 41.85). The incidence was more in age group below 45 years.

The overall mortality from bacteraemia was 18%. Bacteraemia associated mortality gradually increased with age and was especially notable after the age of 45 (Table 2). The mortality among patients over the age of 45 years was 26.31% compared with 12.90% for patients 45 years of age or less. The mortality among male 18.33% (11/60)] and female [17.5% (7/40)] was almost equal.

Out of 100 cases, the incidence of monomicrobial bacteraemia was 95 and polymicrobial was 5. The mortality rate in polymicrobial septicaemia was 3 out of 5 (60%), which was higher than monomicrobial septicaemia (15.78%). Among monomicrobial bacteraemic patients, the incidence was more below the age of 45 years and the mortality was more in patients aged >45years. The incidence and mortality was more in polymicrobial bacteraemic patients aged >45 years (Table 2). The most common organism isolated from monomicrobial bacteraemia and polymicrobial bacteraemia were gram negative bacilli (Table 1).

Table 1: Organisms isolated from blood culture.

Organisms isolated	Total number	Mortality
Monomicrobial bacteraemia		
Pseudomonas aeruginosa	16	6
Salmonella spp.	17	-
Klebsiella spp.	11	3
Acinetobacter spp.	9	0
Citrobacter spp.	7	1
E. coli	7	1
Enterobacter spp.	1	1
Staphylococcus aureus	9	1
Streptococcus pneumoniae	9	1
Enterococcus spp.	5	0
Coaugulase Negative Staphylococcus (CoNS)	4	1
Polymicrobial bacteraemia		
Acinetobacter spp. and Enterococcus spp.	1	1
Acinetobacter spp. and Streptococcus pneumoniae	1	1
Enterococcus spp. and Klebsiella spp.	1	1
Staphylococcus aureus and Klebsiella spp.	1	0
Acinetobacter spp. and Citrobacter spp.	1	0

Table 2: Age wise distribution of incidence and mortality in monomicrobial and polymicrobial bacteraemia.

	Monomicrobial		Polymicrobial	
Age	**Incidence**	**Mortality**	**Incidence**	**Mortality**
18 - 30	29	2	-	-
31 – 45	32	6	1	-
46 – 60	19	3	2	1
61 onwards	15	4	2	2

X^2 = 3.2, P> 0.05

Factors potentially related to the outcome of bacteraemia were nosocomial acquisitions, age >45 years, bacteraemia caused by some difficult to treat organisms, such as Pseudomonas spp. and polymicrobial bacteraemia (Table 3). Mortality was high with polymicrobial infection.

The incidence of primary blood stream infection was seen in 25 cases and secondary blood stream infection was seen in 75 cases.

In Secondary blood stream infection, the most common source of bacteraemia was gastrointestinal tract (27) followed by respiratory tract (22), wound [11], urinary tract (10) and I. V. catheters (5). Mortality in primary and secondary blood stream infections were 12% (3/25) and 20% (15/75). Out of 15 mortality cases, respiratory tract was source of infection in 4 cases, wound in 4 cases, urinary tract in 2 cases, GIT in 4 cases and I. V. catheter in 1 cases.

The organisms isolated from primary blood stream infection in patients who died were S. aureus, Enterococcus spp, Klebsiella spp. and Acinetobacter spp. In secondary blood stream infection, Streptococcus pneumoniae and Pseudomonas aeruginosa were the most common organisms isolated from respiratory tract. Staphylococus aureus was the common organism isolated from I V device. Pseudomonas aeruginosa was the most common organism isolated from wound infection. Enterococcus spp., E.coli and Citrobacter spp. were common organisms isolated from urinary tract. The most common organism isolated from GIT (stool sample) was Salmonella spp.

The source of Pseudomonas bacteraemia in patients who died, were wound infections (burns, surgery), respiratory tract infection and urinary tract infections. Respiratory tract was the only source of Streptococcus pneumoniae bacteraemia in patients who died.

Table 3: Risk factors and their association with mortality.

Risk Factors	Number of cases	Mortality
Nosocomial infection	58	15
Age > 45years	38	10
Polymicrobial infection	5	3
Pseudomonas infection	16	6

The common predisposing factors were recent surgery, Diabetes, cancer, burns, HIV, cirrhosis and neutropenia respectively (Table 4). Nearly 2/3(66 cases) of the patients had no predisposing factors and 32 patients had one predisposing factor. 2 patients had two or more predisposing factors (Diabetes and cancer, cancer and surgery). Mortality was greater among the patients with multiple predisposing factors [1/2 (50%)] than among patients with only a single factor [11/32(34.37%)]. Patients without any predisposing factor had the lowest septicaemia associated mortality [5/66(7.57%)].

Table 4: Patients with one predisposing factor and its association with mortality.

Predisposing Factors	Incidence (n = 32)	Mortality	P value.
Burn	3	3	P = 0.0002
Cancer	4	2	P = 0.0121
Diabetes	7	3	P = 0.0071
Surgery	13	3	P = 0.0577
Neutropenia	1	0	-
HIV	3	0	-
Cirrhosis	1	0	-

The clinical presentation of patients was compared with mortality. It was observed that in patients with 2 criteria the mortality rate was 15.38% and with 3 or more criteria's mortality was 18.92%.(Table 5).

Table 5: Patients presentation and its association with

Presentation	Total number	Mortality
a + b + c + d	17	2
a + b + c	30	4
b + c + d	13	4
a + c	11	2
a + b	10	-
b + c	2	-
a + c + d	3	3
b + d	3	2
a + b + d	11	1

$X^2 = 0.3153$

a)a = Temperature c) c = Respiratory rate
b)b = Pulse rate d) d = Leukocyte count.

Table 6 shows association of total leukocyte count with the mortality in bacteraemic patients. It was observed that the mortality was more in patients with leukocyte count >12,000 /L (29.73%) and <4,000 /L (25%) when compared to patients with leukocyte count between 4,000–11,999/L (9.09%).

Mortality among patients with hospital acquired bacteraemia [15/58(25.86%)] was more than community acquired bacteraemia [3/42(7.14%)]. Among hospital acquired infections the incidence of primary and secondary blood stream infections were 31.1%(18/58) and 68.9%(40/58) respectively. Mortality among primary and secondary blood stream infection was 16.6% and 30% respectively.

Table 6: Association of total leukocyte count with mortality.

Total leukocyte count	Total	Mortality
< 4,000	8	2
4,000 – 11,999	55	5
> 12,000	37	11

$X^2 = 6.639, P < 0.05$

The most common organism isolated from hospital acquired infections was Pseudomonas aeruginosa. Salmonella spp. was the most common organism isolated from community acquired infections (Table 7).

Table 7: Organisms associated with hospital and community acquired infection.

Organisms	Hospital acquired	Community acquired	Z value, P value
Staphylococcus aureus	9	1	Z = 2.468, P<0.05
CoNS	4	-	
Streptococcus pneumoniae	3	7	Z = 1.783, P>0.05
Enterococcus spp.	5	2	Z = 0.769. P>0.05
Pseudomonas aeruginosa	15	1	Z = 3.779, P<0.001
Enterobacter spp.	1	-	
Citrobacter spp.	6	2	Z = 1.062, P>0.05
Salmonella spp.	-	17	
Klebsiella spp.	6	7	Z = 0.913, P>0.05
E coli	5	2	Z = 0.769, P>0.05
Acinetobacter spp.	6	6	Z = 0.582, P>0.05

4. Discussion

A total of 298 adult patients with clinical diagnosis of septicaemia were studied. Blood culture was positive in 100 patients giving overall bacteriological positive septicaemia in 33.55%. Positive blood culture rates vary from 20 to 40 percent of cases of sepsis [2] and our findings are therefore consistent with other studies [9]. Positivity rates of blood cultures vary depending on severity of sepsis and underlying causes.

Bacteraemia associated mortality gradually increased with age and was especially notable after the age of 45. Similar observation was made by Salive ME et al. [10]. Age thus plays a major role in mortality due to septicaemia. Mortality also depends on the severity of patients underlying disease. Mortality among cases with bacteraemia due to gram negative organisms was more than gram positive organisms whereas other studies [11, 12] have found an increased risk of mortality associated with infection due to gram positive organisms. In our study, the result may be because of susceptibility of gram positive organisms to the routinely used antibiotics. The higher mortality recorded in other studies[11,12,13] may be partly related to the recent increase in the prevalence of resistance to antimicrobial agents in gram positive species recorded world wide, for which therapeutic options are more limited than for infections due to gram negative species. Inadequate antimicrobial therapy is an important determinant of outcome in critically ill patients with Blood stream infection(BSI). [14, 15]. Several studies [16,17] conducted in the 1960s and 1970s showed that appropriate antimicrobial therapy leads to lower mortality in patients with gram-negative bacteremia compared with similar patients receiving inappropriate therapy. In contrast, Bryan et al [18] showed that early antibiotic selection for the first 24 hours did not affect survival, regardless of the appropriateness of the antibiotics selected. However, this latter study showed improved survival in patients receiving appropriate antibiotics after the first day of therapy. More recently, Ibrahim et al [15] showed the favorable impact of early adequate antibiotic treatment on outcome of patients with ICU-acquired BSI. Similarly, other studies demonstrated that inadequate antimicrobial treatment was an independent risk factor of mortality for patients with BSI [19].

Among other factors potentially related to the outcome of bacteraemia were nosocomial acquisitions, bacteraemia caused by some difficult to treat organisms, such as Pseudomonas spp. and polymicrobial bacteraemia. Similar observations were made by other workers [7,20].

Pseudomonas aeruginosa was the second most common gram negative organism isolated and mortality rate was also high. Pseudomonas aeruginosa is a highly evolved nosocomial pathogen that is prevalent in the hospital environment and is highly pathogenic in burn patients, contributing considerably to morbidity and mortality [24, 26]. Pseudomonas aeruginosa showed resistance to commonly used antibiotics like tobramycin, piperacillin, cefoperazone, ciprofloxacin and ceftazidime. Blood stream invasion and dissemination of Pseudomonas from local sites of infection is probably mediated by some of the same cell associated and extracellular products responsible for more localized disease. In addition to the possible antiphagocytic properties of the mucoid exopolysacharide and of lipopolysaccharides contained in the outer cell membrane, Pseudomonas isolates are usually resistant to the direct bactericidal activity of serum. Athough Pseudomonas is susceptible to IgM, optimal bacterial clearance requires specific IgG antibodies, intact classic and alternative complement pathways and adequate functioning polymorphonuclear leukocytes. These stringent demands on the host immune system may be increased by the immunoglobulin cleaving and complement inactivating actions of Pseudomonas proteases, providing possible mechanism for the removal of these two important impediments to blood stream invasion [22].

Out of 3 patients who died of polymicrobial bacteraemia, one patient was diabetic; the other two patients didn't have any predisposing factors. The primary sources of infection in these patients were respiratory tract (1), GIT (1), and one case it was unknown. The organisms isolated were Enterococcus spp, Acinetobacter spp, Klebsiella spp, Streptococcus pneumoniae and Citrobacter spp. There was no mortality in patients with monomicrobial bacteraemia due to Acinetobacter spp and Enterococcus spp, where as mortality was seen in polymicrobial cases from where these organisms were isolated. This shows that polymicrobial infection is associated with poorer outcome than monomicrobial infection, independently of the patients underlying disease or the class of microorganisms causing the infection [7,20,11,23]. The lower mortality rate in monomicrobial septicaemia has been explained by Weinstein MP and his colleagues [24]. It was found that patients with monomicrobial septicaemia were more likely than those with polymicrobial septicaemia to be treated with appropriate therapy especially after susceptibility test results were available. Appropriate antimicrobial therapy must cover all organisms identified in cases of polymicrobial infection [24].

The inability to determine the focus of bacteraemia is a vexing problem. Despite substantial advances in diagnostic imaging once the past 2 decades, 25% of bacteraemic episodes in this study had no discernible primary focus. Other studies have noted similar results [25]. In other cases, the most common source of bacteraemia was gastrointestinal tract (27%) followed by respiratory tract (22%), wound (11%), urinary tract (10%) and I. V. catheters (5%). Among the Enterobacteriaceae, primary foci of infection below the diaphragm predominated, as would be expected given the normal habitat of these bacteria. In contrast, the most common foci for bacteraemia due to Pseudomonas aeruginosa was respiratory tract and wound infections (burns, surgery).

The common predisposing factors were surgery, diabetes, cancer, burns, HIV, cirrhosis and neutropenia. The mortality was more in burn patients. A burn injury causes tissue necrosis and raw areas with serous exudation. The devitalized tissue and most burn wounds are favourable for the colonization and proliferation of microorganisms and subsequent infection, therefore the potential risk of burn wound sepsis and septicaemia persists until complete wound healing [21]. Severe burns cause defects in both cellular and humoral immunity that have a major impact on infection [2]. The influence of predisposing factors on the outcome of septicaemia was analysed both when individual factors were present alone and when multiple factors were present. Nearly 2/3 of the patients had no predisposing factors and these patients had the lowest septicaemia associated mortality. There was a direct relationship between septicaemia associated mortality and the number of predisposing factors present. Thus, mortality was greater among the patients with multiple predisposing factors than among patients with only a single factor. Similar findings were observed in other studies [24, 26].

It was observed that in patients with 2 criteria the mortality rate was 15.38% and with 3 or more criterias mortality was 18.92%. Similar results were observed in study by Rangel – Fraurt MS [9]. The clinical signs (eg, high fever) lack the desirable diagnostic power to discriminate between infected and uninfected patients. Therefore, numerous attempts have been made throughout the past 20 years to improve the early diagnosis of sepsis in critically ill patients. Procalcitonin in particular seems to be a promising indicator of sepsis in critically ill patients, capable of complementing clinical signs and routine laboratory variables suggestive of severe infection [27]. Thus, adding procalcitonin to the standard workup of critically ill patients with suspected sepsis could increase diagnostic certainty and improve antibiotic management.

In order to determine whether certain indicators might assist in assessing the clinical significance of positive blood cultures, we examined the relationship between positive culture and leukocyte count. It was observed that patients who had leukocyte count of <4,000 / L or >12,000 / L have an increased relative risk of death. Other studies [25] in varied patient groups with leukocyte count of < 4,000 / L or >12,000 / L have found twofold increase in relative risk of death from septicaemia. Pseudomonas aeruginosa was the common organism isolated from burn patients and mortality was 100% in these patients. This may be because the Pseudomonas aeruginosa isolated were multi drug resistant.

Mortality among patients with hospital acquired bacteraemia (25.86%) was more than community acquired bacteraemia (7.14%). Mortality was more in hospital acquired infection because of

1) Increased incidence of Pseudomonas aeruginosa bacteraemia in hospital acquired infection. Pseudomonas aeruginosa was resistant to commonly used antibiotics.
2) Frequent use of intravascular devices in hospitalized patients.
3) Wound infection (surgical and burns), pneumonia and Urinary tract infection are common nosocomial infections, which lead to bacteraemia. The source of infection may predict death [20].

No mortality was seen in patients with bacteraemia due to Salmonella spp, because strains isolated were sensitive to most of the commonly used antibiotics. All the patients were between the age group of 18-32 years where immunity is well developed. There were no risk factors in these patients, which would affect the immunity of patients.

Several limitations of this study merit consideration. First, the study population was only adults, so the results may not be representative of pediatric ICUs. The observational nature of this investigation does not allow us to draw an absolute causal relationship between exposure to inadequate antimicrobial therapy and death. Despite these limitations, this study provides important epidemiologic information about the occurrence of BSI in critically ill patients, which remains a common and frequently fatal condition. Moreover, we identified several factors affecting survival that must be taken into account for use in future therapeutic trials.

5. Conclusion

Awareness of the risk factors, clinical signs and symptoms, pathophysiology, and updates in the management of sepsis can enhance the nursing care for patients with severe sepsis to promote best practices for sepsis care in the intensive care unit. This finding emphasizes the urgent need for quick diagnostic kits at the bedside [28, 29]. In the case of bacteraemia, this would ideally identify the microorganism on the same day as the blood sample is taken and would allow immediate appropriate antibiotic coverage. Molecular diagnosis using polymerase chain reaction is not yet a standard technique for detection of viable bacteria in the blood. Despite the use of automated processing, the polymerase chain reaction method is time-consuming, labor intensive, and expensive compared with standard culturing methods.

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