Risk Factors for Mortality of Nosocomial Bacteraemia in Intensive Care Units

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Key Words

Nosocomial bacteraemia · *Klebsiella pneumoniae* ·
Methicillin-resistant *Staphylococcus aureus*

Abstract

Objective: The aim of this study was to follow critically ill patients prospectively in intensive care units (ICUs) to determine risk factors for mortality and outcome associated with nosocomial bacteraemia (NB). **Subjects and Methods:** A case-control study of 176 patients was conducted to identify the risk factors for mortality of NB in ICU patients. The study was performed in emergency, surgical and general surgical ICUs with 23 beds during a 15-month period. A total of 1,450 patients were admitted to the ICUs during the study period. The USA Center for Disease Control and Prevention definitions were used to diagnose nosocomial infections. Nosocomial bacteraemia was defined as the isolation of one or more organisms from blood cultures taken at least 48 h after admission, which were not related to a problem present on admission. An assessment of whether the isolated organisms represented true bacteraemia rather than contamination was made by clinical or laboratory evidence of infection. **Results:** A total of 214 bacteraemia episodes were found in the 176 patients (64 female, 112 male; 51.3 ± 21.3 years old), 90 of whom died and 86 survived. The bacteraemia rate was 12.1%. The most common etiological agents of bacteraemia

were *Klebsiella pneumoniae*: 46 (21.5%), methicillin-resistant *Staphylococcus aureus*: 46 (21.5%), *Pseudomonas aeruginosa*: 32 (14.9%), and *Escherichia coli*: 20 (9.3%). Multivariate analysis showed that the requirement of mechanical ventilation for more than 7 days ($p < 0.001$), total parenteral nutrition ($p = 0.034$), inotropic drug ($p < 0.001$), and increased creatinine level ($p = 0.034$) were independent risk factors for mortality of NB in ICUs. **Conclusions:** Nosocomial infections caused by Gram-negative bacteria continue to be one of the major sources of morbidity and mortality.

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Introduction

Patients in the intensive care units (ICU) are at a higher risk of acquiring nosocomial infections compared with patients in general wards [1, 2]. This is partly because of the severity of the underlying illnesses and partly because of iatrogenic factors related to the high frequency of invasive procedures required for monitoring and treatment [3].

Bacteraemia continues to be a major cause of morbidity and mortality in hospitals. In ICU, Gram-negative bacilli are responsible for a considerable percentage of all nosocomial bacteraemia (NB) [4]. The overall or crude rate of death does not distinguish between the contribu-

tion of the patients' underlying diseases and the contribution of bloodstream infections [5]. The prognosis of post-bacteraemia infection (true bacteraemia or fungaemia) is very variable. In recent years, many studies have analyzed the mortality rates in relation to pathogens, source of infection, patient age, and underlying diseases. This study was carried out to identify the risk factors for mortality and outcome associated with NB in ICU.

Subjects and Methods

This cohort study was conducted prospectively for 15 months. The study was performed in ICUs of Emergency, Surgery and General Surgery of the Istanbul Faculty of Medicine Hospital with 23 beds between 1 October 2001 and 31 December 2002. A total of 1,450 patients were admitted to the ICUs during the study period and included solid organ and bone marrow transplant recipients. A case-control study was conducted to identify the risk factors for mortality of NB in ICU patients. The USA Center for Disease Control and Prevention (CDC) definitions were used to diagnose nosocomial infections [6, 7].

NB was defined as the isolation of one or more organisms from blood cultures taken at least 48 h after admission that were not related to a problem present on admission. An assessment of whether or not the isolated organisms represented true bacteraemia rather than contamination was made by clinical or laboratory evidence of infection: fever, hypothermia, evidence of a localized infection, inadequate organ perfusion, severe sepsis, leukocytosis, or laboratory findings compatible with disseminated intravascular coagulopathy.

Blood cultures (BaC/Alert, Organon Teknika, Durham, N.C., USA) were generally taken from the patients in ICU only when systemic infection was suspected. The culture bottles were incubated at 37°C and tested for a minimum of 7 days. The isolation of bacteria from two or more bottles was accepted as significant. All isolated micro-organisms were identified by standard laboratory methods [8, 9]. Antimicrobial susceptibility tests were performed as indicated by NCCLS M2-A7 and M100-S11 [10, 11].

Severity of illness was measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sepsis-Related Organ Failure Assessment (SOFA) scores. The following data collected for each patient were recorded: age, sex, main diagnostic categories leading to ICU admission, hospital and ICU admission dates, ICU admission diagnosis, need for and duration of mechanic ventilation, presence of central vascular catheter, presence of leukopenia (total leukocyte count <4,000/ μ l), requirement of total parenteral nutrition, inotropic drug (dopamine, dobutamine, adrenaline, noradrenaline) and haemodialysis on admission, broad-spectrum antibiotic use in the previous 2 weeks, length of stay in ICU, presence of diabetes mellitus, malignancy, organ failure, solid organ or bone marrow transplantation, immunosuppressive therapy (on admission or within the past 45 days), trauma and surgery. All haematological and biochemical values were also included in the analysis. All patients, who were discharged from the ICU, were followed for 30 days.

Data were obtained during the daily visits of the patients in accordance with 50 variables (clinical, microbiological, and course-related). The source of bacteraemia was established depending on clinical and microbiological findings.

Severe sepsis was defined as systolic blood pressure <90 mm Hg associated with at least one of the following conditions: confusion, oliguria (<30 ml/h), hypoxaemia (pO_2 <70 mm Hg), acidosis (pH <7.3), or analytical findings compatible with disseminated intravascular coagulation.

Frequency, percentage, ratio and categorical variables were analyzed with a χ^2 test. Student's t test and Mann-Whitney U test were performed to analyze continuous variables. Significant univariate predictors ($p \leq 0.05$) of risk factors for NB were included in a logistic regression model to identify the independent predictors. Multivariate analysis was conducted with a logistic regression. Ninety-five percent confidence intervals (95% CI) were calculated for all significant predictors. Statistical significance was defined as a $p \leq 0.05$ [12].

Results

Two hundred and fourteen bacteraemia episodes occurred in the 176 patients (64 female, 112 male; 51.3 ± 21.3 years old), of whom 90 (51.1%) died and 86 (48.9%) survived. The bacteraemia rate for each patient was 12.1%. Of the 214 bacteraemic episodes, 125 (58.4%) were Gram-negative bacilli, and there were 82 (38.3%) episodes of Gram-positive cocci and 7 (3.3%) of *Candida* spp. The most common Gram-negative etiological agents were *Klebsiella pneumoniae* ($n = 46$; 21.5%), *Pseudomonas aeruginosa* ($n = 32$; 14.9%), *Escherichia coli* ($n = 20$; 9.3%), while the most frequent Gram-positive pathogens were methicillin-resistant *Staphylococcus aureus* ($n = 46$; 21.5%), methicillin-resistant coagulase-negative staphylococci ($n = 18$; 8.4%), methicillin-sensitive *S. aureus* ($n = 11$; 5.4%), and *Enterococcus faecium* (table 1).

In first bacteraemic episodes, mortality occurred in 35 (16.4%) cases of bacteraemia with Gram-negative bacilli and 24 (11.2%) with Gram-positive cocci. Thirty-one (14.5%) patients (15 Gram-negative bacteria, 12 Gram-positive cocci, and 4 *Candida* spp.) with two episodes died (table 2).

With regard to nosocomial infections causing bacteraemia, nosocomial pneumonia ($n = 62$; 29%), primary bloodstream infection ($n = 48$; 22.4%), surgical site infection ($n = 38$; 17.8%), and soft tissue infection ($n = 12$; 5.6%) were the most frequent diseases (table 3).

Considering mortality, 32 patients with nosocomial pneumonia, 23 patients with primary bloodstream infection, 16 patients with surgical site infection (mostly organ/space infection), and all bacteraemic patients with mediastinitis, endocarditis, meningitis, endometritis)

Table 1. Micro-organisms isolated from blood cultures and bacteraemic episodes

Infectious agents	Episodes		
	one	two	three
Gram-negative bacilli (n = 125)			
<i>Klebsiella pneumoniae</i> (n = 46; 21.5%)	38	4	–
<i>Pseudomonas aeruginosa</i> (n = 32; 14.9%)	26	3	–
<i>Escherichia coli</i> (n = 20; 9.3%)	14	3	–
<i>Acinetobacter baumannii</i> (n = 11; 5.14%)	8	–	1
<i>Enterobacter</i> spp. (n = 7; 3.3%)			
<i>E. cloacae</i>	6	–	–
<i>E. sakazaki</i>	1	–	–
<i>Proteus</i> spp. (n = 6; 2.8%)			
<i>P. mirabilis</i>	1	–	–
<i>P. vulgaris</i>	1	2	–
<i>Klebsiella oxytoca</i> (n = 3; 1.4%)	3	–	–
Gram-positive cocci (n = 82)			
Methicillin-resistant <i>Staphylococcus aureus</i> (n = 46; 21.5%)	31	6	1
Methicillin-resistant coagulase-negative staphylococci (n = 18; 8.41%)	12	3	–
Methicillin-sensitive <i>Staphylococcus aureus</i> (n = 11; 5.14%)	8	–	1
<i>Enterococcus</i> spp. (n = 7; 3.3%)			
<i>E. faecium</i>	5	–	–
<i>E. faecalis</i>	2	–	–
Others			
<i>Candida</i> spp. (n = 7; 3.3%)	3	2	–

Table 2. Bacteraemic episodes and mortality rates

Infectious agents	Mortality related to bacteraemic episodes	
	one episode (n = 159)	two episodes (n = 46)
Gram-negative bacilli (n = 125)	35 (16.4%)	15 (7%)
<i>Pseudomonas aeruginosa</i>	14 (6.5%)	6 (2.8%)
<i>Klebsiella pneumoniae</i>	10 (4.7%)	7 (3.3%)
<i>Escherichia coli</i>	4 (1.9%)	2 (0.9%)
<i>Acinetobacter baumannii</i>	4 (1.9%)	–
<i>Enterobacter cloacae</i>	1 (0.47%)	–
<i>Proteus mirabilis</i>	1 (0.47%)	–
<i>Enterobacter sakazaki</i>	1 (0.47%)	–
<i>Proteus vulgaris</i>	–	–
<i>Klebsiella oxytoca</i>	–	–
Gram-positive cocci (n = 82)	24 (11.2%)	12 (5.6%)
MRSA	15 (7.01%)	10 (4.7%)
MSSA	5 (2.3%)	2 (0.9%)
MRCNS	2 (0.9%)	–
<i>Enterococcus faecium</i>	2 (0.9%)	–
<i>Enterococcus faecalis</i>	–	–

MRSA = Methicillin-resistant *S. aureus*; MRCNS = methicillin-resistant coagulase-negative staphylococci; MSSA = methicillin-sensitive *S. aureus*.

Table 3. Sites of nosocomial infections caused by bacteraemia

Nosocomial infections	Number of deaths ¹	Mortality rates ²	
		within 21 days	within between 22 and 30 days
Nosocomial pneumonia (n = 62; 29%)	32 (14.9%)	25 (11.7%)	7 (3.3%)
Primary bloodstream infection (n = 48; 22.4%)	23 (10.7%)	20 (9.3%)	3 (1.4%)
Surgical site infection ³ (n = 38; 17.8%)	16 (7.5%)	8 (3.74%)	8 (3.74%)
Soft tissue infection (n = 12; 5.6%)	–	–	–
Intra-abdominal infection (n = 11; 5.1%)	5 (2.3%)	5 (2.3%)	–
Symptomatic urinary tract infection (n = 9; 4.2%)	1 (0.5%)	1 (0.5%)	–
Mediastinitis (n = 4; 1.9%)	4 (1.9%)	4 (1.9%)	–
Endocarditis (n = 3; 1.4%)	3 (1.4%)	3 (1.4%)	–
Meningitis (n = 2; 0.9%)	2 (0.9%)	2 (0.9%)	–
Endometritis (n = 2; 0.9%)	2 (0.9%)	2 (0.9%)	–
Lymphangitis (n = 2; 0.9%)	2 (0.9%)	–	1 (0.5%)
Skin infection (n = 10; 4.6%)	–	–	–
Decubitus ulcer infection (n = 8; 3.7%)	–	–	–
Osteomyelitis (n = 3; 1.4%)	–	–	–

¹ Mortality rates were calculated by considering bacteraemic episodes.

² Mortality was related to NB and directly or indirectly to severe sepsis.

³ Organ/space (n = 23) and deep incisional (n = 15).

Table 4. Univariate analysis of risk factors for mortality of NB

	Survivors (n = 90)	Nonsurvivors (n = 86)	p value
Age, years	45.4 ± 19.6	56.8 ± 21.4	>0.5
Duration of hospitalization, days	20.05 ± 17.25	20.9 ± 20.1	>0.5
Trauma	25 (29.1%)	20 (22.2%)	0.3
Leukopenia	1 (1.2%)	6 (6.7%)	0.1
Diabetes mellitus	9 (10.5%)	14 (15.6%)	0.3
Solid organ transplantation	4 (4.7%)	2 (2.2%)	0.4
Immunosuppression	6 (7%)	11 (12.2%)	0.3
Surgery	37 (43%)	38 (42.2%)	1
Broad-spectrum antibiotic use in previous 2 weeks	64 (74.4%)	62 (68.9%)	0.5
MV more than 7 days	27 (31.4%)	62 (68.9%)	<0.001
Haemofiltration	13 (15.1%)	30 (33.3%)	0.005
Total parenteral nutrition	8 (9.3%)	35 (38.9%)	<0.001
Inotropic drugs	7 (8.1%)	35 (7.2%)	<0.001
Malignant hypertension	8 (9.3%)	21 (23.3%)	0.01
Duration of central venous catheterization, days	10.5 ± 11.5	15.2 ± 14.5	0.019
Leukocyte count, µl	17,277 ± 21,068	25,315 ± 46,728	0.1
Aspartate aminotransferase, U/l	41.5 ± 42.2	118.45 ± 245.7	0.005
Alanine aminotransferase, U/l	34.2 ± 36.5	101.5 ± 218.1	0.006
Increased creatinine level, mg/dl	1.42 ± 1.1	2.1 ± 1.26	0.001
Haemoglobin level, g/dl	10.5 ± 2.06	9.5 ± 1.8	0.000
Platelet count, /µl	220,398 ± 291,154	158,466 ± 125,381	0.07
APACHE II scores ¹	7.76 ± 5.19 (2–23; 6)	13.27 ± 5.26 (2–29; 12)	0.000
SOFA scores ¹	5.8 ± 4.1 (2–20; 4)	11.39 ± 3.8 (1–18; 12)	0.000
Glasgow Coma Scale ¹	13.34 ± 2.4 (2–19; 14)	11.31 ± 2.75 (6–15; 12)	0.000

Values are given as number or mean ± SD. MV = Mechanical ventilation.

¹ Values in parentheses represent range and median.

died. However, bacteraemic patients with all soft tissue infections, skin infection and osteomyelitis survived (table 3).

The risk factors for mortality in patients with bacteraemia were malignant hypertension ($\chi^2 = 6.3$, $p = 0.01$), requirement of mechanical ventilation for more than 7 days ($\chi^2 = 24.7$, $p < 0.001$), prolonged use of central vascular catheter ($\chi^2 = 65.3$, $p = 0.019$), having a haematological malignancy or solid tumour ($\chi^2 = 9.4$, $p = 0.002$), increased creatinine level (>1.4 mg/dl; $\chi^2 = 7.9$, $p = 0.005$), haemofiltration ($\chi^2 = 6.4$, $p = 0.007$), requirement of total parenteral nutrition ($\chi^2 = 20.8$, $p < 0.001$) and inotropic drug on admission ($\chi^2 = 28.2$, $p < 0.001$). The mean values of APACHE II scores, SOFA scores and Glasgow Coma Scale in surviving patients with bacteraemia were significantly different from those of other patients ($p < 0.001$ for all variables) (table 4).

Multivariate analysis showed that requirement of mechanical ventilation of more than 7 days [odds ratio (OR): 6.8, $p < 0.001$], requirement of total parental nutrition (OR: 3.1, $p = 0.034$), requirement of inotropic drug (OR: 12.8, $p < 0.001$), and increased creatinine level (OR: 2.7, $p = 0.034$) were independent risk factors for mortality of NB in ICUs (table 5).

Discussion

S. aureus, antibiotic-resistant Gram-negative bacteria, and *Candida* spp. are among the pathogens responsible for bloodstream infections, which are usually associated with the poorest outcomes [13, 14]. In recent years, the number of Gram-negative bacilli causing nosocomial infections has increased because of their ability to express certain resistance phenotypes [15] and hence they continue to be one of the major sources of morbidity and mortality [16, 17]. While in these studies the most frequently isolated pathogens that caused NB infections were *Klebsiella* spp., *Candida* spp., *Enterococcus* spp. and *P. aeruginosa*, in our study they were *K. pneumoniae*, methicillin-resistant *S. aureus*, *P. aeruginosa* and *E. coli*.

Pneumonia, as a source of secondary bacteraemia, has been reported to be more frequent among patients with NB acquired in ICU [18]. Additionally, pneumonia has also been reported as a frequent source of NB [17, 19]. However, primary bloodstream infection, in which no source could be determined, was also reported to be the most frequent source of NB [20]. A probable explanation why pneumonia is a common source of NB are lower re-

Table 5. Multivariate analysis of risk factors for mortality of NB

Predictors	OR	95% CI	p value
MV more than 7 days			
+	6.8	2.5–18.4	<0.001
–	1.0		
Total parenteral nutrition			
+	3.1	1.1–9.1	<0.03
–	1.0		
Inotropic drug			
+	12.8	4.4–37.7	<0.001
–	1.0		
Creatinine level			
Increased	2.7	1.1–72	<0.03
Normal	1.0		
MV = Mechanical ventilation.			

spiratory tract infections [4]. Nosocomial pneumonia has also been reported to be a major risk factor for mortality [21, 22] similar to the findings of our study. However, *P. aeruginosa* and *K. pneumoniae* were the responsible pathogens in the fatal cases with NB.

The use of broad-spectrum antibiotics was not a risk factor for mortality in our study (table 4) but Trouillet et al. [23] identified the duration of mechanical ventilation before the occurrence of nosocomial pneumonia, prior antibiotic use, and prior use of broad-spectrum drugs (i.e., imipenem, third-generation cephalosporin, and/or fluoroquinolone) as being independently associated with infection due to antibiotic-resistant bacteria. Broad-spectrum antibiotic use was found to be the most important risk factor associated with the occurrence of this undesirable medical practice.

Nosocomial infection, nosocomial pneumonia, older age, high APACHE II score, mechanical ventilation, enteral nutrition, tracheostomy and use of steroids or chemotherapy were found to be the most important risk factors for mortality in ICU [24–26] similar to our study and those of others [27–30].

Conclusions

Nosocomial infections caused by Gram-negative bacteria continue to be one of the major sources of morbidity and mortality.

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