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Risk factors for mortality in patients with nosocomial *Staphylococcus aureus* bacteremia*

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Aim: Bloodstream infections (BSIs) due to *Staphylococcus aureus* have become increasingly common in hospitals worldwide. The aim of this study was to evaluate the risk factors for mortality of nosocomial BSI due to *S. aureus*.

Materials and methods: We analyzed risk factors for mortality of methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteremia in a prospective case control study in a 1196-bed tertiary referral medical center. Logistic regression analyses were used to determine risk factors and prognostic factors of mortality.

Results: Between July 2006 and January 2009, 176 patients were identified with clinically significant and microbiologically confirmed nosocomial bacteremia due to *S. aureus*. After controlling potential risk factors for mortality on multivariate logistic regression analysis, age equal to and greater than 60 years, hospitalization in intensive care unit, total parenteral nutrition support, and methicillin resistance were found as independent risk factors for mortality. The mortality with MRSA bacteremia was revealed to be 3.02 times higher than that of MSSA bacteremia (P = 0.008, RR = 3.02, 95% CI = 1.34–6.8).

Conclusion: *S. aureus* BSI is a serious condition and methicillin resistance leads to higher mortality rates.

Key words: *Staphylococcus aureus*, bacteremia

Introduction

Despite vast improvements in medical care and the development of new antimicrobial agents, sepsis remains a serious condition. The incidence of sepsis varies according to patients' characteristics and the complexity of medical care (1–3). Mortality due to bloodstream infections (BSIs) is high, ranging from 12% to 81%, depending on the population (1,4,5). Early diagnosis of bacteremia is very important for reducing the mortality rate by implementing adequate treatment before the onset of severe sepsis and septic shock.

In recent years, BSIs due to gram-positive cocci have increased (6–9). Although effective antistaphylococcal drugs are available, *Staphylococcus aureus* bacteremia has high incidence and mortality rates, and methicillin resistance may influence clinical outcome (6,10–12) *S. aureus* is responsible for 50% to 87% of nosocomial bacteremias, and the mortality rate ranges from 16% to 43% (1,13–15).

The aim of the present prospective case control study was to evaluate the risk factors for mortality among patients with nosocomial *S. aureus* bacteremia.

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Materials and methods

Patients

All patients ≥18 years old with 1 or more positive blood cultures for *S. aureus* were identified by review of the results of blood cultures performed during the study period at the microbiology laboratory of the 1196-bed tertiary referral medical center. If the same patient developed *S. aureus* bacteremia (SAB) more than once, only the first episode (if clinically compatible with *S. aureus* bacteremia) was included in the study, and further episodes were recorded for assessing persistence or recurrence. Patients were followed until discharge from the hospital or death.

Hospital and design

This prospective case control study was conducted in a tertiary teaching hospital in Turkey between July 2006 and January 2009. Once the positive blood cultures for *S. aureus* were identified by the microbiology laboratory, patients were visited. Patients' functional status, demographic characteristics, comorbid conditions, and other possible risk factors for mortality of nosocomial SAB were recorded. Data for each patient were collected according to a previously established protocol.

Data collection

Collected data included for patients with nosocomial SAB were: age, sex, admission diagnosis (e.g., infection, malignancy, trauma, burn), underlying diseases (e.g., diabetes mellitus, chronic renal failure, chronic lung disease, immunosuppression), intensive care unit (ICU) stay, mental status of patients, septic shock, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, support of total parenteral nutrition (TPN) or enteral nutrition, use of invasive devices (central venous catheter, endotracheal tube, mechanical ventilator, nasogastric tube, peripheral arterial line, hemodialysis catheter, Foley catheter, drainage tube), surgical operation, duration of hospital stay, antimicrobial susceptibility results, methicillin resistance, prior antibiotic exposure, appropriate antibiotic therapy, bacteremia type (primary, catheter related, secondary), persistence, recurrence, and patient outcome.

The APACHE II score was calculated on the basis of a long-term health evaluation and a set of acute physiologic parameters obtained during the first 24 h of ICU admission.

Definitions

BSI was defined as a positive blood culture for *S. aureus* with clinical signs and symptoms of infection. *S. aureus* BSI was considered as nosocomial onset when a positive blood culture was obtained after the first 48 h of hospitalization in a patient with no symptoms or signs of infection at the time of hospital admission (16).

Bacteremia was classified using the guidelines of the Centers for Disease Control and Prevention. If bacteremia with no primary focus was determined or if it existed before such a focus appeared, it was considered to be a primary bacteremia. Catheter-associated bacteremia was diagnosed when inflammatory signs were observed at the catheter insertion point or when culture of the catheter tip was positive for *S. aureus*. Secondary bacteremia was diagnosed if a focal infection was observed prior to the onset of bacteremia, focal symptoms and signs were present, or *S. aureus* was isolated from the focus of infection (17,18).

Persistent bacteremia was defined as the isolation of *S. aureus* in blood cultures obtained from peripheral veins for ≥7 days despite appropriate antibiotic therapy administration for ≥5 days (19). Recurrence was diagnosed if *S. aureus* was isolated in blood culture although 14 days appropriate antibiotic therapy had been administered for the first *S. aureus* BSI and negative blood culture had been detected.

Appropriate antibiotic therapy was defined when the initial antibiotic exhibited in vitro activity against the *S. aureus* strain isolated, when it was used in correct dosage and within 3 days after the onset of bacteremia.

A prior antibiotic exposure was defined as the administration of antibiotics for more than 48 h within 60 days preceding SAB. *S. aureus* BSI was considered as primary when the source of BSI could not be found (20–22).

ICU-associated bacteremia was defined when the bacteremia was diagnosed after 48–72 h from admission of the patients to the ICU units.

The crude mortality was defined as the ratio of the number of patients who died with nosocomial SAB to the total number of patients with the bacteremia (7).

Statistical analysis

Data were stratified to analyze the association with mortality. Continuous variables are described as mean ± standard deviation (SD) and median (interquartile range). Chi-square tests were used for categorical variables and Student's t-tests were used for continued variables. Logistic regression analysis of variables associated with mortality was performed. $P < 0.05$ was considered significant. Covariates that were found to be significant ($P < 0.05$) in univariate analysis were included in logistic regression analysis. All statistical analyses were processed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Odds ratios and 95% confidence intervals (95% CI) were calculated.

Results

From July 2006 through January 2009, we identified 176 patients with clinically significant and microbiologically confirmed nosocomial *S. aureus* BSI, 102 of which had methicillin-resistant *S. aureus* (MRSA) BSI, and 74 of which had methicillin-susceptible *S. aureus* (MSSA) BSI. The demographic and clinical characteristics of patients are summarized in Table 1. Of the study patients, 71 (40.3%) were ≥60 years old, 121 were male (68.7%), 122 (69.3%) had 1 or more underlying diseases, and 49 (27.8%) had ≥2 underlying diseases.

Among the *S. aureus* isolates, 58% (n = 102) were methicillin-resistant, and all samples were susceptible to vancomycin. The sources of *S. aureus* bacteremia were as follows: primary bacteremia was detected in 75.6% patients (n = 133), and 27.3% of the study patients had intravascular catheter-related bacteremia. Secondary bacteremia was detected in 24.4% of the patients. Persistent bacteremia occurred in 19 patients (10.8%). Prebacteremia antibiotic usage was higher in patients with MRSA bacteremia (82%) than in patients with MSSA bacteremia, and the difference was statistically significant ($P < 0.001$, RR = 14.5, 95% CI = 6.9–30.4).

The total mortality rate of the study patients was 49.4% (87/176). The mortality rate in the first 14 days was 29% (51/176) (Table 2). In univariate analysis, 11 variables were associated significantly with death: age equal to and greater than 60 years, ICU hospitalization, length of ICU stay, ICU-associated bacteremia,

Table 1. Demographic and clinical characteristics of patients with nosocomial *S. aureus* bacteremia.

Characteristics		**n**	**%**
Age			
	<60 years	105	59.7
	≥60 years	71	40.3
Sex			
	Male	121	68.7
	Female	55	31.3
Admission diagnosis			
	Infection	18	10.2
	Malignancy	43	24.4
	Trauma	11	6.3
	Burn	17	9.7
	CNS pathology	33	18.8
	GIS pathology	20	11.4
	CVS pathology	7	4.0
	Chronic renal insufficiency	10	5.7
	Others	17	9.7
Underlying diseases		122	69.3
≥2 underlying diseases		49	27.8
Wards			
	Service	102	58.0
	ICU	74	42.0

CNS = central nervous system, GIS = gastrointestinal system, CVS = cardiovascular system, ICU = intensive care unit.

Table 2. Methicillin resistance, bacteremia type, and outcomes of patients with nosocomial *S. aureus* bacteremia.

Strain		n	%
	MSSA	74	42.0
	MRSA	102	58.0
Source			
Primary		133	75.6
Catheter related		48	27.3
Secondary		43	24.4
Persistent bacteremia		19	10.8
Recurrent bacteremia		2	1.1
14-day outcome			
	Survival	125	71.0
	Death	51	29.0
Outcome			
	Survival	89	50.6
	Death	87	49.4

MSSA = methicillin-sensitive *S. aureus*, MRSA = methicillin-resistant *S. aureus*.

septic shock, unconsciousness, previous antibiotic usage before the onset of bacteremia, resistance to methicillin, secondary BSI to pneumonia, presence of invasive devices (TPN, mechanical ventilator, endotracheal tube, Foley catheter), and surgery before the onset of bacteremia (Table 3). Enteral feeding, primary diagnosis, comorbidity, and appropriate therapy were not found to be associated with death.

The mean age ± SD of the study patients who died in the hospital after the onset of nosocomial *S. aureus* bacteremia was 57.7 ± 18.1 years, which was associated significantly with mortality (P = 0.005, 95% CI = 2.6–13.7). The mean total length of hospitalization stay of the study patients who died in hospital was 37.7 ± 33.4 days; the average APACHE II score of these patients was 15.9 ± 7.0. Except for older age (age equal to and greater than 60 years), there was no statistically significant association between other selected continuous variables and mortality (P > 0.05).

The crude mortality rate of *S. aureus* bacteremia was 50.6%. The difference between the mortality rates of MRSA (62.7%) and MSSA bacteremia (31.0%) was 31.7%. Upon multivariate logistic regression analysis, the mortality rate with MRSA bacteremia was revealed to be 3.02 times higher than with MSSA bacteremia (P = 0.008, RR = 3.02, 95% CI = 1.34–6.8). The other risk factors for mortality on multivariate logistic regression analysis were older age (≥60 years old), ICU hospitalization, and TPN support (Table 4).

Table 3. Univariate analysis of the mortality risk factors of patients with nosocomial *S. aureus* bacteremia.

Characteristics	Death n (%)	Survival n (%)	P	RR	95% CI
Age			**0.015**	**2.13**	**1.1–3.9**
<60 years (n = 105)	44 (41.9)	61 (58.1)			
≥60 years (n = 71)	43 (60.6)	28 (39.4)			
Wards			**0.000**	**5.6**	**2.9–10.9**
Service hospitalization	33 (32.4)	69 (67.6)			
ICU hospitalization	55 (74.3)	19 (25.7)			
Infection source					
Hospital-associated (n = 113)	41 (36.3)	72 (63.7)	0.000	4.7	2.4–9.3
ICU-associated (n = 63)	46 (73.0)	17 (27.0)	**0.000**	**4.75**	**2.41–9.33**
*Septic shock (n = 10)	10 (100.0)	0 (0.0)	**0.01**		
Unconsciousness (n = 49)	37 (75.5)	12 (24.5)	**0.000**	**4.75**	**2.2–10.0**
TPN (n = 57)	45 (78.9)	12 (21.1)	**0.000**	**6.79**	**3.24–14.2**
Enteral feeding (n = 32)	19 (59.4)	13 (40.6)	>0.05		
Invasive procedure					
Endotracheal tube (n = 33)	28 (84.8)	5 (15.2)	**0.000**	**7.97**	**2.9–21.8**
Mechanical ventilator (n = 49)	37 (75.5)	12 (24.5)	**0.000**	**4.74**	**2.3–10.0**
Foley catheter (n = 92)	59 (64.1)	33 (35.9)	**0.000**	**3.58**	**1.2–6.7**
Surgery (n = 56)	34 (60.7)	22 (39.3)	**0.04**	**1.92**	**1.0–3.7**
Lung infiltration (n = 58)	38 (65.5)	20 (34.5)	**0.03**	**2.76**	**1.4–5.1**
Prior antibiotic usage (n = 106)	61 (57.5)	45 (42.5)	**0.008**	**2.3**	**1.2–4.3**
Methicillin resistance (n = 102)	64 (62.7)	38 (37.3)	**0.000**	**3.73**	**2.0–7.0**

ICU = intensive care unit, RR = relative risk, 95% CI = 95% confidence interval, GIS = gastrointestinal system, CNS = central nervous system, CVS = cardiovascular system, COPD = chronic obstructive pulmonary disease, TPN = total parenteral nutrition.
*Because all of the patients with septic shock died, OR and 95% CI could not be calculated.

Table 4. Statistically significant parameters for mortality of patients with nosocomial *S. aureus* bacteremia that were found by logistic regression analysis.

Independent variables		P	RR	95% CI
Age		**0.002**	**1.03**	**1.01–1.06**
Wards		**0.002**		
	Service location		**1**	
	ICU location		**6.25**	**1.91–20.46**
TPN		**0.017**		
	No		1	
	Yes		**3.29**	**1.24–8.76**
Bacteremia type		**0.008**		
	MSSA		**1**	
	MRSA		**3.02**	**1.34–6.8**

RR = relative risk, CI = confidence interval, ICU = intensive care unit, MSSA = methicillin-sensitive *S. aureus*, MRSA = methicillin-resistant *S. aureus*.

Discussion

Nosocomial BSIs are important causes of morbidity and mortality. *S. aureus* remains an important cause of nosocomial BSI. In the present study, we analyzed risk factors for mortality in nosocomial bacteremia due to *S. aureus* in our hospital. Bacteremia due to *S. aureus* had been previously reported to be associated with mortality rates of 15%–60% (11,23,24). In our study the mortality rate within 14 days after *S. aureus* bacteremia was 29%. Day 14 was chosen as the cut-off because several authors have suggested that death due to bacteremia occurs early, rarely after the second week (1). The crude hospital mortality among patients with nosocomial *S. aureus* bacteremia was found to be 49.4%. Comparing the characteristics of survivors to those who died during their hospital stay elicited several significant differences (Table 4). In some series, overall BSI-associated mortality has been reported to be greater than 50% in older adults (25,26). Our results offer further evidence that older age is an independent predictor of mortality associated with nosocomial *S. aureus* BSI. These results suggested that the mortality was 2.13 times higher in patients who were ≥60 years old (P = 0.015, RR = 2.13, 95% CI = 1.1–3.9). The mortality rate among ICU patients was 74.3% (n = 55) (P = 0.000, RR = 5.6, 95% CI = 2.9–10.9). In our study, ICU-associated bacteremia affected patients' outcome, leading to a 4.75-fold increased rate of death (P < 0.001, RR = 4.75, 95% CI = 2.41–9.33). These findings are consistent with previous studies, which have documented an independent association between acquisition of infection in an ICU and mortality (27,28). By univariate analysis, we also found that septic shock (P = 0.01) and unconsciousness were significant risk factors for death. Since all of the patients with septic shock had died, RR and 95% CI could not be calculated. In the univariate analysis, invasive procedures such as central venous catheter, endotracheal tube, and mechanical ventilator were found as significant risk factors for mortality, but these parameters were not statistically significant with logistic regression analysis. Cevik et al. (29) investigated the relationship between nosocomial infection and mortality in a neurology intensive care unit in Turkey. They found TPN to be a risk factor for mortality (P < 0.0001). Consistent with the study of Cevik et al., we showed that TPN was an independent risk factor for mortality in nosocomial *S. aureus* BSI (P = 0.000, RR = 6.79, 95% CI = 3.24–14.2). Although we know that enteral feeding is better than parenteral nutrition when appropriate, we did

not find it to be significant in this study (P > 0.05) (Table 3). It is important to note that enteral feeding should be preferred to TPN support whenever possible. Regarding the prognostic importance of the source of bacteremia, only the respiratory focus was associated with a significantly higher mortality rate in the univariate analysis (P = 0.03, RR = 2.76, 95% CI = 1.4–5.1). The higher mortality associated with this source of infection is consistent with previous published studies (1,30), although this result did not persist after controlling for other confounders in the multivariate analysis in our study. We found 57.5% crude mortality among patients who had used antibiotics before the onset of bacteremia, which was a statistically significant risk factor for mortality in univariate analysis (P = 0.008, RR = 2.3, 95% CI = 1.2– 4.3). However, it was not found to be an independent risk factor with logistic regression analysis. Consistent with Karchmer's study (8), we found that prebacteremia antibiotic usage is a risk factor for methicillin resistance (P < 0.001, RR = 14.5, 95% CI = 6.9–30.4). This is why it can be found as a risk factor for mortality in univariate analysis. After controlling the other potential risk factors for mortality on multivariate logistic regression analysis, it was not statistically significant. Given the results of the prior study of Blot et al. (31), we expected to find a higher rate of death among patients who had higher APACHE II scores, but this did not affect the mortality rates in statistical analysis in our study. We calculated APACHE II scores on the day of admission to ICU. The bacteremia was diagnosed in the patients who died at median day 14.5 (range: 0–123 days) of ICU admission. We did not calculate APACHE II scores on the day of the bacteremia diagnosis; this is a limitation of our study. This could be the reason that APACHE II score was not found as a statistically significant risk factor in our study. BSI due to MRSA may account for up to 50% of all staphylococcal BSIs (32,33). In the present study, 58% of the study patients had nosocomial MRSA BSI. Today there are still doubts about the effect of methicillin resistance on mortality due to the *S. aureus* BSIs. Previous studies comparing outcomes in MSSA and MRSA bacteremia revealed some conflicting results. Differences could be due to the different populations of patients and types of treatments or specific microbiological characteristics of the strains isolated in different countries. Despite ongoing controversy about the relatively high mortality rate among patients with MRSA BSI, several studies have concluded that BSI due to MRSA had higher mortality rates (1,34,36). Previous metaanalysis also had results similar to these studies (13,31). In our study, patients with MRSA bacteremia had a higher mortality rate (62.7%) compared with MSSA bacteremia (31%). Logistic regression analysis showed that methicillin resistance was an independent risk factor for death (P = 0.008, RR = 3.02, 95% CI = 1.34–6.8).

In conclusion, age equal to and greater than 60 years, ICU hospitalization, TPN support, and methicillin resistance were found as independent risk factors for mortality due to the *S. aureus* BSIs in this study. TPN and methicillin resistance, which were found as independent risk factors for mortality due to the *S. aureus* BSIs, can be changeable factors due to the use of infection control measures.

Since the major mode of transmission of MRSA from patient to patient is through the contaminated hands of health care workers, hand hygiene is very important to prevent cross-contamination. As in other previous studies, Alp et al. (37) showed the clonal spreads of MRSA in an ICU. Candevir et al. (38) showed that the MRSA rate decreased from 89.6% in 2006 to 61.8% in 2009 (P < 0.001) in their study. They thought that the decrease in MRSA rates was the result of decreased cross-contamination via decreased *S. aureus* rates among causatives (from 14.5% in 2006 to 4.5% in 2009). An effective infection control program is needed to prevent MRSA infection. Active surveillance of newly admitted patients for MRSA and rapid and effective isolation and treatment may help control the spread of MRSA infections. The hand hygiene compliance of health care workers and standard precautions are important infection control measures to control MRSA in endemic settings. For decreasing methicillin resistance, we also decided to evaluate rational antibiotic usage.

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