Article/Artigo

Methicillin-resistant *Staphylococcus aureus* bloodstream infection: risk factors and clinical outcome in non-intensive-care units

Infecção de corrente sanguínea por *Staphylococcus aureus* resistente à meticilina: fatores de risco e evolução clínica em unidades não críticas

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ABSTRACT

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) is spread out in hospitals across different regions of the world and is regarded as the major agent of nosocomial infections, causing infections such as skin and soft tissue pneumonia and sepsis. The aim of this study was to identify risk factors for methicillin-resistance in *Staphylococcus aureus* bloodstream infection (BSI) and the predictive factors for death. **Methods:** A retrospective cohort of fifty-one patients presenting bacteraemia due to *S. aureus* between September 2006 and September 2008 was analysed. *Staphylococcu aureus* samples were obtained from blood cultures performed by clinical hospital microbiology laboratory from the Uberlândia Federal University. Methicillin-resistance was determined by growth on oxacillin screen agar and antimicrobial susceptibility by means of the disk diffusion method. **Results:** We found similar numbers of MRSA (56.8%) and methicillin-susceptible *Staphylococcus aureus* (MSSA) (43.2%) infections, and the overall hospital mortality ratio was 47%, predominantly in MRSA group (70.8% vs. 29.2%) (p=0.05). Age (p=0.02) was significantly higher in MRSA patients as also was the use of central venous catheter (p=0.02). The use of two or more antimicrobial agents (p=0.03) and the length of hospital stay prior to bacteraemia superior to seven days (p=0.006) were associated with mortality. High odds ratio value was observed in cardiopathy as comorbidity. **Conclusions:** Despite several risk factors associated with MRSA and MSSA infection, the use of two or more antimicrobial agents was the unique independent variable associated with mortality.

Keywords: *Staphylococcus aureus.* MRSA. Bacteraemia. Risk factors.

RESUMO

Introdução: *Methicillin-resistant Staphylococcus aureus* (MRSA), se disseminou nos hospitais em diferentes regiões do globo, e é atualmente o principal agente de infecções hospitalares causando infecções de pele, tecidos moles, pneumonia e sepse. O objetivo deste estudo foi identificar fatores de risco para resistência à meticilina em infecções de corrente sanguínea por *Staphylococcus aureus* e fatores preditivos de mortalidade. **Métodos:** Uma coorte de 51 pacientes apresentando bacteremia por *S. aureus,* entre setembro de 2006 a setembro de 2008 foi analisada. Amostras de *S. aureus* foram obtidas a partir de hemoculturas realizadas pelo laboratório de microbiologia do hospital de clínicas da Universidade Federal de Uberlândia. A resistência à meticilina foi determinada pelo crescimento no agar triagem para oxacilina e a sensibilidade aos antimicrobianos pelo método de difusão em agar. **Resultados:** Infecções por MRSA (56,8%) e *methicillin-susceptible Staphylococcus aureus* (MSSA) (43,2%) foram similares e a taxa de mortalidade hospitalar foi de 47%, predominantemente no grupo infectado por MRSA (70,8% vs. 29,2%) (p=0,05). Idade (p=0,02) e a presença de cateter vascular central (p=0,02) foram significantes no grupo de infectados por MRSA. A evolução demonstrou que o uso de dois ou mais agentes antimicrobianos (p=0,03) e tempo de internação prévio à bacteremia superior a sete dias (p=0,006) foram associados à morte. Altos valores de *odds ratio* foram observados para cardiopatia como comorbidade. **Conclusões:** Embora vários fatores de risco tenham sido associados a infecções por MRSA e MSSA e mortalidade o uso de dois ou mais agentes antimicrobianos foi a única variável independente para mortalidade.

Palavras-chaves: *Staphylococcus aureus.* MRSA. Bacteremia. Fatores de risco.

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INTRODUCTION

A broad variety of infections, ranging from minor infections of the skin to severe infections as bloodstream infections, can be caused by *Staphylococcus aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an endemic nosocomial pathogen, but its geographic spread in the community has been documented[1]. Some previous studies of patients with MRSA bloodstream infection (BSI) have reported higher mortality rates, increased morbidity, and longer hospital length of stay than those with methicillin-susceptible *Staphylococcus aureus* BSI[2,3]. In the UK, MRSA infection is cited with increasing frequency as causing or contributing to death[4,5]. Risk factors for methicillin-resistance in these infections have been extensively described, but the studies vary among institutions[6,7].

Methicillin-resistance among *S. aureus* remains an important problem in Latin America hospitals[8], but rates vary significantly from hospital to hospital. In Brazil, the Antimicrobial Surveillance Program (SENTRY)[9] described a prevalence of MRSA bacteraemia of 30.9% in hospitalized patients between 1997 and 2000, but in large Brazilian teaching hospitals, up to 73% of clinically significant *S. aureus* bacteraemia were caused by methicillin-resistant strains. Ribas et al.[10] reported 49.5% of bloodstream infection in Clinical Hospital of Uberlândia's Federal University due to *S. aureus*, and recently, Carvalho and Gontijo Filho[11] described 63.7% of *S. aureus* BSI due to MRSA in adult critical-care unit.

The objectives of this study were to identify institution-specific risk factors for methicillin-resistance in *S. aureus* BSI to determine the predictive factors for death and assess the impact of methicillin-resistance on mortality in patients in non-intensive-care units of a Brazilian University Hospital.

METHODS

The study was conducted in a 500-bed teaching hospital that provides tertiary care for Uberlândia and surroundings. The investigation was designed as a retrospective cohort of patients presenting bacteraemia due to *S. aureus*. Clinical and epidemiological data were collected from the hospital patient records.

Bloodstream infections were classified as primary when they were not related to any other focus of infection. BSIs were considered to be secondary when they were clinically related to infection in another site than the vascular system[12]. Previous antimicrobial therapy was defined as the use of any antibiotic within 30 days prior to bacteraemia[13]. Antimicrobial therapy was considered to be adequate if the drug used within the first 48h after blood culture collection had *in vitro* activity against the isolated *S. aureus* strain[13]. Bacteraemia-associated mortality was characterized by the patient's death during the bacteremic episode and/or 30 days after hospitalization period without any other explanation[14].

Hemocultures were performed by inoculating 5-10mL of blood into a flask of the automatic commercial system Bactec/Alert® (Vitek system). Positive cultures were further sub-cultured in Müeller-Hinton Agar (Isofar Ltda, Brazil) supplemented with 5% of human blood and incubated for 24-48h at 35 ± 2°C in the hospital microbiology laboratory. Methicillin-resistance was determined by growth on oxacillin screen agar and antimicrobial suscetibility by means of the disk diffusion method with disks containing antimicrobial agents.

Univariate analysis was used to compare variables for the outcome groups of interest. Continuous variables were compared using Student's *t* test for normally distributed variables. The χ^2 statistic or Fisher´s exact test was used to compare categorical variables. Multivariate analysis was performed using multiple logistic regression with stepwise approach for entering new terms into the BioEstat5.0 model with 0.2 as the limit for their acceptance or removal. All p values lower than 0.2 were considered significant.

Ethical considerations

The present study was approved by the Ethics Committee of Federal University of Uberlândia (UFU) (014/06).

RESULTS

Between September 2007 and September 2008, 134 *S. aureus* BSIs were identified. Methicillin-resistance rate was 59.7% (80/134). Among these cases, 83 were excluded from the study because of incomplete or missing data. A total of 51 episodes in 39 patients were then reviewed. Ten patients presented multiple episodes of MRSA BSI, and two presented multiple episodes of MSSA BSI. Thirty-one infections occurred in male patients, and twenty occurred in female patients (**Table 1**).

Table 1 shows clinical and demographic characteristics of patients with MRSA and MSSA BSI. Methicillin-resistant *Staphylococcus aureus* bloodstream infection occurred in older patients, after a longer time following admission when compared with MSSA BSI. All Methicillin-resistant *Staphylococcus aureus* bloodstream infection were classified as nosocomial. The use of more than two antimicrobial agents, comorbidity, and length of hospital stay prior to bacteraemia longer than seven days were more frequent in MRSA group. Presence of intravascular device was significantly higher in MRSA group than in MSSA group. The sources of *S. aureus* BSI are also listed in **Table 1,** and in both, MRSA and MSSA, primary BSIs were the most common sources than secondary ones, and 22 (75.9%) of whom with MRSA episodes were associated with central venous catheter.

TABLE 1 - Clinical and demographic characteristics of patients with MRSA and MSSA BSIs.

Characteristics	MRSA n = 29 (56.8%)	MSSA n = 22 (43.2%)	Odds ratio (CI)	p (≤0.05)
Mortality	17 (58.6)	7 (24.1)	3.036 (0.949 - 9.719)	0.057
Age (years), median (range)	56.13 (0-89)	39.6 (0-80)		0.021
Sex (female/male)	11/18	9/13	0.882 (0.284 - 2.743)	0.829
LOS before BSI (days), median (range)	46.4 (0-300)	13.7 (0-74)		0.074
Origin onset				
community-acquired	0	2 (9.0)	0.139 (0.006 - 3.051)	0.181
nosocomial	29 (100.0)	20.0 (91.0)		
Prior hospitalization antimicrobial therapy	14 (48.3)	12.0 (54.5)	0.777 (0.255 - 2.364)	0.657
no	2	4	0.333 (0.055 - 2.016)	0.389
yes	27	18		
≥2	19	9	2.744 (0.874 - 8.618)	0.080
Comorbidity	27 (93.1)	18 (81.8)	3.000 (0.496 - 18.14)	0.382
diabetes	4 (14.8)	3 (16.6)	1.013 (0.202 - 5.079)	1.000
cardiopathy	9 (31.0)	3 (16.6)	2.850 (0.668 - 12.15)	0.192
pulmonary disease	3 (11.1)	2 (11.1)	1.154 (0.175 - 7.579)	1.000
nefropathy	2 (7.4)	1 (5.5)	1.556 (0.131 - 18.35)	1.000
malignancy	3 (11.1)	5 (27.7)	0.392 (0.082 - 1.861)	0.267
others	6 (22.2)	4 (22.2)	1.174 (0.287 - 4.798)	1.000
Surgery	16 (55.2)	14 (63.6)	0.703 (0.225 - 2.191)	0.543
Presence of central venous catheter unit	22 (75.9)	10 (45.5)	3.771 (1.141 - 12.46)	0.026
ITU	1 (3.5)	1 (4.5)	0.750 (0.044 - 12.70)	1.000
surgical	5 (17.3)	4 (18.2)	0.720 (0.158 - 3.269)	0.712
clinical	10 (34.5)	5 (22.7)	1.789 (0.508 - 6.293)	0.361
pediatrics	1 (13.5)	2 (9.0)	0.357 (0.030 - 4.217)	0.571
others	12 (41.4)	10 (45.4)	0.847 (0.276 - 2.592)	0.771
Source				
primary	21 (72.4)	19 (86.4)	0.357 (0.030 - 4.217)	0.571
secondary	8 (27.6)	3 (13.6)	2.413 (0.557 - 10.44)	0.311
Length of hospital stay prior to bacteraemia				
>7 days	23 (79.3)	12 (54.5)	3.194 (0.933 - 10.93)	0.059
<7 days	6 (20.7)	10 (45.5)	0.313 (0.091 - 0.575)	0.059
Initial antimicrobial therapy				
inadequate	10 (34.5)	7 (31.8)	1.128 (0.346 - 3.670)	0.841
adequate	19 (65.5)	15 (68.2)	0.886 (0.272 - 2.885)	0.845

MRSA: methicillin-resistant *Staphylococcus aureus;* **MSSA:** methicillin-susceptible *Staphylococcus aureus*; **BSI:** blood stream infection; **CI:** confidence interval; **LOS:** length of hospital stay; **ITU:** intensive-therapy unit.

TABLE 2 - Potential prognostic death factors associated with *Staphylococcus aureus* bacteraemia.

	Outcome n = 51					
	death n=24(47.0)		survival n=27(53.0)			
Factors associated	**n**	**%**	**n**	**%**	**Odds ratio (CI)**	**p (≤0.05)**
Sex						
female	11	45.8	9	33.3	1.692 (0.544 - 5.259)	0.361
male	13	54.2	18	63.0		
Age (years)						
≥60	13	54.2	8	29.6	2.807 (0.88 - 8.88)	0.075
≤60	11	45.8	19	70.4		
Origin onset						
community-acquired	0	0.0	2	7.4	0.208 (0.009 - 4.56)	0.491
nosocomial	24	100.0	25	92.6		
Susceptibility to meticillin						
resistant	17	70.8	12	44.4	3.035 (0.949 - 9.709)	0.057
sensitive	7	29.2	15	55.6	0.3294 (0.1030 - 1.0533)	0.109
Antimicrobial therapy						
no	2	8.3	3	11.0		
yes	22	91.7	24	89.0		
≥2	16	72.7	10	41.6	2.744 (0.874 - 8.618)	0.034
Initial antimicrobial therapy						
inadequate	10	41.6	7	25.9	2.041 (0.625 - 6.663)	0.234
adequate	14	58.4	20	74.1	0.490 (0.150 - 1.600)	0.234
Comorbidity	22	91.6	20	74.1	3.85 (0.714 - 20.75)	0.146
diabetes	4	18.2	3	15.0	1.60 (0.319 - 8.01)	0.693
cardiopathy	5	22.7	4	20.0	1.51 (0.355 - 6.443)	0.718
pulmonary disease	3	13.7	0	0.0	8.95 (0.438 - 183.0)	0.097
nefropathy	0	0.0	4	20.0	0.106 (0.005 - 2.092)	0.112
malignancy	5	22.7	3	15.0	2.105 (0.445 - 9.950)	0.450
others	5	22.7	6	30.0	0.921 (0.241 - 3.516)	1.000
Surgery	15	62.5	15	55.5	0.777 (0.229 - 2.635)	0.686
Presence of central venous catheter unit	16	66.6	16	59.3	1.375 (0.437 - 4.319)	0.585
ITU	1	4.0	1	3.7	1.130 (0.066 - 19.13)	1.000
surgical	5	20.8	4	14.8	1.513 (0.355 - 6.443)	0.718
clinical	11	45.8	5	18.5	3.457 (0.988 - 12.09)	0.046
pediatrics	2	8.6	4	14.8	0.522 (0.086 - 3.149)	0.671
others	5	20.8	13	48.2	0.283 (0.081 - 0.980)	0.041
Length of hospital stay prior to bacteraemia						
>7 days	21	87.5	14	51.8	6.500 (1.561 - 27.06)	0.006
<7 days	3	12.5	13	48.2	0.153 (0.036 - 0.640)	0.007

CI: confidence interval; **ITU:** intensive therapy unit.

The overall mortality rate was 47%. Univariate analysis for potential prognostic death factors associated with *S. aureus* bacteraemia is presented in **Table 2**. The presence of MRSA (p=0.057), clinical status, represented by patient´s unit (p=0.046), and length of hospital stay prior to bacteraemia higher than seven days (p=0.006) were significantly associated with death. No difference was found regarding sex, age, severity of underlying disease, nosocomial origin of the infection, or presence of intravascular device among the patients who died compared with the patients who survived.

In multivariate analysis (**Table 3**), the use of more than two antibiotics was independently associated with mortality by *S. aureus* (OR=8.65; 95% CI=1.92 to 39.07; p=0.05). ORs observed for long duration of hospital stay (OR=4.7) and cardiopathy (OR=5.85) were both high in death patients group.

TABLE 3 - Multivariate analysis for mortality by *Staphylococcus aureus* bacteraemia.

Variable	Odds ratio	95% CI	p
More than two antimicrobial agents	8.655	1.92 to 39.07	0.005
MRSA infection	0.500	0.11 to 2.24	0.361
Cardiopathy	5.851	0.91 to37.51	0.062
Presence of intravascular device	0.888	0.20 to 3.98	0.876
Length of hospital stay prior to bacteraemia			
>7 days	4.716	0.79 to 27.99	0.087

CI: confidence interval; **MRSA:** methicillin-resistant *Staphylococcus aureus*.

DISCUSSION

Hospital-acquired bloodstream infections caused by *S. aureus*, mainly those due to methicillin-resistant *S. aureus* (MRSA), are associated with significant mortality and morbidity[15], adding considerable costs to hospital care[16]. In Brazil, *S. aureus* was the most common cause of bloodstream infection (20.2%), and resistance to methicillin was observed in 31% of *S. aureus* isolates in the Brazilian hospital participating in the SENTRY Antimicrobial Surveillance Programme[9]. However, MRSA rates may vary greatly among hospitals (55.9-73%)[8,13]. In our hospital, bacteraemia rates caused by MRSA were both high in both critical (63.7%) and non-critical units (62.5%)[11]. In our study, we observed a similar rate (56.8%) of BSI due to MRSA in clinical, burned, and oncology wards, and almost all BSIs (96%) had nosocomial origin.

The emergence of MRSA is largely due to the dissemination of clonal strains between patients favored for poor infection control politics and antimicrobial pressure[17], but this correlation has been difficult to establish due to the high number of variables involved[18]. Risk factors for methicillin resistance reported in literature also vary among institutions and patients. The major independent risk factors include: advanced age[19,20], residence in a nursing home[7,21], long duration of hospitalization[4], prior antibiotic exposure[6,22], insulin-requiring diabetes[23], intravascular devices[3,24], presence of decubitus ulcers or pneumonia as source of BSI[6,15,24], inadequacy of antimicrobial therapy, and severity of clinical status[13].

In the present study, based on univariate analysis, age and presence of central venous catheter (CVC) were risk factors for MRSA bacteraemia as also reported previously[10,13]. Most (72.4%) of MRSA bacteraemia were classified as primary, and CVC was probably the foci of infection as discussed by Das et al.[24]. A high proportion of these infections were detected in clinical ward (34.5%), while most studies reported higher MRSA infections in critical-care units[24,25].

Other analyzed variables such as length of hospital stay prior to bacteraemia (OR=3.19), cardiopathy as comorbidity (OR=2.85), and more than two antimicrobial drugs usage (OR=2.74), despite having no significance, presented high OR values when compared with MRSA and MSSA infections. Several studies also have demonstrated that longer hospitalization before the onset of bacteraemia[25] and antimicrobial use in greater frequency[10] were risk factors for MRSA infection. None of these factors — age, central vascular catheter presence or even the use of more than two antimicrobial drugs, cardiopathy, or longer hospital stay prior to bacteraemia — were independently prognostic factors for MRSA infection in our study.

Comparisons of mortality between patients with MRSA and MSSA have been contradictory in the literature[15]. Several studies including a meta-analysis have demonstrated an increase in mortality among patients with MRSA bacteraemia versus MSSA bacteraemia[3,4,26,27]. In this study, a higher crude mortality of 58.6% vs 24.1% (OR=3.036; p=0.05) was observed in the MRSA group than the MSSA group, respectively, a higher rate than those reported in United Kingdom and United States hospitals[15,27].

Traditional risk factors for mortality include older age[10,15,28], inadequate treatment[13,29], and severity of comorbidity[25]. Despite the fact that these variables were not significant in our study, we attribute an association between these risk factors and mortality due to the high OR values of 2.80, 2.04, and 3.85, respectively. Intensive-care unit admission before bacteraemia is also a predictor for MRSA-BSI mortality[15,24]. Most of the deaths due to staphylococcal BSI occurred in the clinical ward (45%; p=0.046), with only 4% of patients carried out in the ICU.

Length of hospitalization is a measure of morbidity[15], as well as invasive device use such as CVC[30]. In the univariate analysis, death was associated with an increase in length of hospital stay for more than seven days (p<0.05) and the use of more than two antimicrobial drugs (p=0.034), but only the former was independently significant (OR=8.65; p=0.005) in multiple regression analysis. In multivariable analysis for the length of hospital stay prior to bacteraemia superior to seven days (OR=4.7) and cardiopathy as comorbidity (OR=5.8), we observed high OR values. These findings coincide with previous reports demonstrating that factors for mortality include: longer of hospital stay before bacteraemia[25] and comorbidities as cardiopathy[31]. Neverthless, in our study, patients with bacteraemia were usually confined in non-critical units due to lack of sufficient beds in the ICU where 33.3% of patients received inadequate empirical antimicrobial therapy that resulted in higher rate (41.6%) of hospital mortality. Eighty percent of the patients who died using an inadequate treatment were from MRSA BSI group.

One of the limitations of the study was that it was done retrospectively and performed at a single hospital.

In addition, the small sample size of the study limited the detection of statistically significant differences. We also did not use the Apache II or other scores to assess severity of illness prognostic indicator on the hospital mortality.

In conclusion, high hospital mortality was observed even in cases of patients who were admitted in non-critical-care units. We found several risk factors associated to MRSA and MSSA bacteraemia and high mortality level of *S. aureus* bacteraemia. However, the use of two or more antimicrobial agents was the unique independent variable for death. This can be partially justified by high frequency of inadequate empirical therapy observed in our study. In spite of the limitations, mainly the small number of patients, the findings suggest an imperative for hospitals to review their antimicrobial policies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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