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Full Length Research paper

Nosocomial methicillin-resistant *Staphylococcus aureus* bacteremia in a tertiary care hospital: Risk factors, overall mortality and antimicrobial resistance

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A retrospective study on risk factors of *Staphylococcus aureus* bacteremia was carried out on 99 blood culture isolated episodes of *S. aureus* in a Brazilian hospital during 2000 - 2002". We found several factors associated with an increased risk of methicillin-resistant *S. aureus* (MRSA) bacteremia including presence of two or more devices and use of antimicrobials. The patients with MRSA bacteremia were most likely to be in the surgical wards, but those with MSSA bacteremia were most likely to be in the internal medical ward. Overall mortality rate was 33.3%. Among 99 patients with episodes of *S. aureus* bacteremia, 25 died (25.3%) within 15 days of onset. Our research shows that MRSA bacteremia was more likely to be associated with extrinsic factors.

Key words: *Staphylococcus aureus* bacteremia, nosocomial MRSA, risk factors, epidemiologic study.

INTRODUCTION

Bloodstream infections (BSIs) are an important cause of death with the mortality rate ranging 25 - 50% (Pittet, 1993). In recent years, BSIs and antimicrobial resistance due to Gram-positive cocci have increased in frequency (Karchmer, 2000; Martin et al., 2003). *Staphylococcus aureus* is a major cause of bacteremia and *S. aureus* bacteremia is associated with higher morbidity and mortality, compared with bacteremia caused by other pa-thogens. The burden of *S. aureus* bacteremia, particularly methicillin-resistant *S. aureus* bacteremia, in terms of cost and resource use is high (Panlilo et al., 1992; NNIS, 1996; Mylotte and Tayara, 2000; van der Mee- Marquet et al., 2004; Naber, 2009). In Latin American, the Antimicro-bial Surveillance Programme (SENTRY) described a prevalence of MRSA bacteremia of 30.9% in hospitalized patients between 1997 and 2000 (Sader et al., 2002).

Different investigators explore the risk factors for MRSA bacteremia (Catchpole et al., 1997; Lowy, 1998) and examine the contribution of methicillin- resistance with respect to clinical outcomes (Harbarth et al., 1998). Several risk factors influencing the outcome of *S. aureus* bacteremia have been identified including the severity of the underlying disease, presence of cardiovascular diseases increased age, acquisition of the infection in the hospital and bacteremia caused by MRSA (Topeli et al., 2000).

In this study, 99 SAB strains isolated in a Brazilian hospital were included to evaluate the clinical characteristics and antibiotic resistance traits to determine the risk factors associated with mortality in patients.

MATERIALS AND METHODS

Setting

The Uberlândia University Hospital is a 503-bed tertiary teaching hospital, in Uberlândia, Minas Gerais.

Study population

Patients with *S. aureus* bacteremia (SAB) were identified by retrospective laboratory based surveillance at the hospital. This study was done while the patients were still in the hospital. Every inpatient with ≥ 1 blood culture positive for *S. aureus* from April/2000 through April/2002 was initially considered for inclusion in this study.

Study design and bacterial identification

This study consisted of a chart review of patients identified by

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Table 1. Portals of entry for *S. aureus* causing bacteremia, stratified by place of acquisition.

Portal of entry	*S. aureus* bacteremia N = 99 (%)
Unknown	19 (19.2)
Intravascular catheter	62 (62.6)
Lung	03 (4.8)
Surgical site	08 (12.9)
Other[1]	07 (7.1)

[1] Skin, abscess, endocarditis, kidney etc.

positive blood cultures in the microbiology laboratory. The medical records of patients identified by surveillance were reviewed for demographic and risk factor data. The colonies were characterized as *Staphylococcus* through Gram staining and catalase test. *S. aureus* identification was made by manitol salt agar fermentation and coagulase tests.

An episode of *S. aureus* bacteremia was defined by blood culture confirmation of organism. Bacteremia was considered to be nosocomial if the > 72 h after admission and there was no clinical evidence of infection on admission (Hugonnet, 2004). Bacteremia was classified as primary when it was unrelated to another focus of infection or when it was related to an intravenous catheter site infection. Bloodstream infections were considered to be secondary when they were clinically related to infection in another site (Guilard et al., 2006). Outcome was classified as death or survival. No attempt was made to determine if death was directly attributable to SAB. Crude mortality rate was defined as the ratio of the observed number of deaths among bacteremic patients during the hospital stay, independent of the cause, divided by the number of patients with bacteremia (Garroust-Orgeas et al., 2000).

Antimicrobial susceptibility test

The test of diffusion in agar was applied according to recommendations of "Clinical and Laboratory Standards Institute (CLSI)" (CLSI, 2006), using Mueller-Hinton Agar (Isofar LTDA, Brazil) and antibiotic disks (OXOID, England). The susceptibility of *S. aureus* was analyzed using disks of cefoxitine (30 g).

Statistical methods

Statistical significance was defined by a p value less than 0.05. The frequencies of qualitative variables were compared using chi-squared with Yates's correction or Fisher's exact test (two-tailed).

Ethical approval

Ethical approval to conduct the study was obtained from the Institutional Ethics Committees of the participating hospital.

RESULTS

There were 99 episodes of *S. aureus* bacteremia available and identified by teaching hospital laboratories from April 2000 to April 2002. Nosocomial bacteremia caused by MRSA were common in the surgical wards (28.0%), but in clinical wards bacteremia by MSSA were more frequent (32.6%).

The primary foci of SAB are listed in Table 1. The source of the bacteremia was unknown in 19.2% of the episodes and in 62.6% of the episodes it was due to an intravascular catheter. In 18.2% of the episodes the bacteremia was considered to be secondary.

Risk factors analysis for *S. aureus* bacteremia are given Table 2. Patients with MRSA bacteremia did not differ from those with MSSA bacteremia in terms of gender and age, but based on statistical analysis, several clinical characteristics were observed with significant difference between MRSA and MSSA, including surgery underwent, invasive devices and use of two or more antimicrobials ($p = 0.005$) mainly vancomycin, cephalosporins $3^a/4^a$ generation and imipenem use. In our study, underlying co-morbidity available was not associated with infection. Overall, 33 (33.3%) of the 99 patients with episodes of SAB died during hospitalization.

Infections by MRSA demand a more rigorous treatment evaluation, including choice of antibiotics, since they relate with greater morbidity and mortality, as compared to those caused by MSSA (Kollef, 2005). Metanalysis studies by Whitby, McLaws and Berry (2001) and Cosgrove et al. (2002), including results from various publications comparing the mortality risk among patients with bacteremia, those by MRSA presented increased mortality, when compared to MSSA-associated infections. In our study, the mortality rate observed was also higher, but without statistical significance in the group with bacteremia by MRSA (38.0%) when compared to that of the group with MSSA (28.6%).

Table 3 shows the results of the univariate analysis to identify predictors of mortality in the study cohort. The risk of death was increased in patients who were ≥ 60 age, had received vancomycin or source primary of SAB. All of the isolates were susceptible to vancomycin and the resistance rates for the MSSA strains were just for erythromycin (16.3 %) and tetracycline (14.3%).

In the present study, the majority of the isolates were resistant to more than 3 antimicrobials (Table 4). Resistance to vancomycin was not observed. These data were similar to those described by Teixeira et al. (1995), when more than 70% of the MRSA isolates from 5 large hospitals located in geographically distant parts of Brazil carried traits of resistance to at least 9 different antibiotics.

Table 2. Clinical characteristics associated with Methicillin-Resistant *Staphylococcus aureus* bacteremia in univariate analysis.

Risk factors	Bacteremia		P	OR (IC)
	MRSA N = 50 (%)	MSSA **N = 49 (%)**		
Age				
more than 60 years	21 (42.0)	19 (38.8)	0.90	1.14 (0.47 - 2.76)
Hospital stay				
more than 7 days	46 (92.0)	40 (81.6)	0.21	2.59 (0.66 - 10.93)
Gender				
Female/Male	18 (36.0) / 32(64.0)	16 (32.7) / 33 (67.3)	0.88	1.16 (0.47 - 2.89)
Surgery	30 (60.0)	13 (26.5)	0.001	4.15 (1.64 - 10.68)
Trauma	06 (12.0)	04 (8.2)	0.74	1.53 (0.35 - 7.04)
Invasive device				
Number more than two	49 (98.0)	43 (87.8)	0.05	6.84 (0.76 - 156 - 7)
Urinary catheter	40 (80.0)	33 (67.3)	0.22	1.94 (0.71 - 5.36)
Endotracheal tubes	20 (40.0)	13 (26.5)	0.22	1.85 (0.73 - 4.72)
Central venous line	38 (76.0)	26 (53.1)	0.02	2.80 (1.10 - 7.25)
Drain	23 (46.0)	08 (16.3)	0.003	4.37 (1.56 - 12.51)
Nasogastric tubes	29 (58.0)	14 (28.6)	0.005	3.45 (1.38 - 8.73)
Antimicrobial use				
Yes	48 (96.0)	43 (87.8)	0.15	3.35 (0.56 - 25.48)
Number more than two	46 (92.0)	33 (67.3)	0.005	5.58 (1.55 - 21.9)
Vancomycin	39 (78.0)	27 (55.1)	0.02	2.89 (1.11 - 7.63)
Cephalosporins $3^a/4^a$ generation	37 (74.0)	24 (49.0)	0.01	2.96 (1.18 - 7.56)
Imipenem	08 (16.0)	01 (2.0)	0.03	9.14 (1.08 - 202-9)
Fluorquinolone	16 (32.0)	13 (26.5)	0.70	1.30 (0.50 - 3.40)
Co-morbidities				
Diabetes	14 (28.0)	19 (38.8)	0.35	0.61 (0.24 - 1.55)
HIV	03 (6.0)	-	0.24	ND*
Cancer	05 (10.0)	08 (16.3)	0.52	0.57 (0.15 - 2.13)
Overall mortality	19 (38.0)	14 (28.6)	0.43	1.53 (0.61 - 3.88)

* Not determined

DISCUSSION

The high proportion of nosocomial *S. aureus* bacteremia caused by methicillin-resistant strains indicates the importance of this organism as a cause of important infection at this hospital. The results of several studies have suggested that MRSA bacteremia has a greater morbidity and mortality than MSSA bacteremia (Selvey et al., 2000). However, our study has not found a difference in virulence between the two, suggesting that MRSA cause similar morbidity and mortality, as observed by other study (Hershor et al., 1992).

In the present study, > 90% of the risk factors was associated with MRSA infection. Based on univariate analysis, we found several factors associated with an increased risk of acquiring MRSA including surgery presence, 2 or more invasive devices including intravascular catheter, drains and nasogastric tubes. Beeston et al. (2009) demonstrated that patients with Staphylococcal infections with MRSA received antimicrobials in greater frequency than those with MSSA. The use of vancomycin was also a strong risk factor for MRSA bacteremia. Therefore, if vancomycin is used empirically for high- risk groups, prompt review of therapy is required once laboratory results are known (Cordova et al., 2004) . Results of this study shows that vancomycin use was high in both groups (78.0 and 55.1%), with significant differences.

Table 3. Prognostic factors for death among 99 episodes of *S. aureus* bacteremia.

Characteristic	Mortality/ total (%)	P
Age (years)		
Less than 60	11/59 (18.6)	0.0003
More than 60	22/40 (55.0)	
Type of bacteremia		
MRSA[1]	19/50 (38.0)	0.43
MSSA[2]	14/49 (28.6)	
Underlying Disease		
Diabetes		
Yes	9/21 (42.9)	0.43
No	24/78 (30.8)	
Cancer		
Yes	07/13 (53.8)	0.11
No	26/86 (30.2)	
Renal Disease		
Yes	08/28 (28.6)	0.69
No	25/71 (35.2)	
Treatment Group		
Vancomycin	27/66 (40.9)	0.04
Cephalosporin	14/65 (21.5)	0.06
Fluorquinolone	10/29 (34.5)	0.93
Source of SAB[3]		
Primary		
Yes	23/81 (28.4)	0.05
No	10/18 (55.6)	
Hospital ward		
Intensive Care Units		
Yes	05/15 (33.3)	0.76
No	28/84 (33.3)	
Surgical		
Yes	13/27 48.1)	0.09
No	20/72 (27.8)	

[1]Methicillin-resistant *S. aureus*, [2]Methicillin-sensitive *S. aureus*, [3]*S. aureus* bacteremia.

Vascular catheter is the most important risk factor for hospital- acquired bacteremia with central venous catheter which associated up to 90.0% of this infection (Darouiche, 2001). In this series 64.6% of patients with *S. aureus* bacteremia were using catheters. The frequency of secondary bacteremia was 18.2% and surgical site was the most frequent focus with 12.9%. The greater role of Staphylococci as a cause of primary nosocomial bacteremia continues and it is a nationwide phenomenon as illustrated elsewhere and it was confirmed in our results being 50.5% of this organism's resistance to oxacillin.

Crude mortality rates of nosocomial bacteremia have varied in different reports ranging from 18 to 33% (Garroust-Orgeas et al., 2000). In the present study, mortality associated with bacteremia due to *S. aureus* was high (33.3%) and this rate was in line with another report (Pittet et al., 1997). Several studies (French et al., 1990; Kuikka and Valtonen, 1994; Conterno et al., 1998;

Table 4. Resistance to antimicrobial agents in MRSA and MSSA isolates.

Antimicrobial	MRSA N= 50 (%)	MSSA N= 49 (%)
Amikacin	45 (90.0)	2 (4.1)
Rifampin	34 (68.0)	4 (8.2)
Erythromycin	46 (92.0)	8 (16.3)
Tetracycline	45 (90.0)	7 (14.3)
Chloramphenicol	46 (92.0)	2 (4.1)
Ciprofloxacin	47 (94.0)	2 (4.1)
Trimethoprim-sulfamethoxazole	46 (92.0)	4 (8.2)
Levofloxacin	29 (58.0)	2 (4.1)
Gentamicin	44 (88.0)	3 (6.1)
Imipenen	45 (90.0)	2 (4.1)
Vancomycin	0 (0)	0 (0)

Romero-Vivas et al., 1995; Harbarth et al., 1998; Mylotte and Tayara, 2000) published in the 1990s have identified risk factors for mortality among patients with SAB. Factors previously found to be significantly associated with mortality include older age (McClelland et al., 1999), source of SAB and SAB caused by MRSA (Conterno et al., 1998), inadequate treatment (Romero-Vivas et al, 1995), acute severity of illness at onset of SAB (Yzerman et al., 1996; Mylotte and Tayara, 2000) and underlying disease status (Kuikka and Valtonen, 1994; Mylotte and Tayara, 2000). In our study, similar risk factors were shown, with prominence to age (≥ 60 years old) and primary source of SAB.

Approximately ¾ of deaths in our study occurred within the first 2 weeks of hospitalization. Similar findings were reported in several studies: 77% of deaths within the first two weeks (Cosgrove et al., 2002), 50% of deaths within 6 days of hospitalization with *S. aureus* bacteremia (Finkelstein et al., 1984) and half of deaths within two days of hospitalization in bacteremia of various causes (Amit et al., 1994).

In the present study, the majority of the isolates were resistant to more than 3 antimicrobials. These data were similar to those described by Teixeira et al. (1995), when more than 70% of the MRSA isolates from 5 large hospitals located in geographically distant parts of Brazil carried traits of resistance to at least 9 different antibiotics.

There are several potential limitations of the present study that should be mentioned. First, we had a relatively small sample size, thus reducing our statistical power and the ability to study subsets of patients. Another limitation of this study was that information on the management of the conditions and the severity of underlying illness (for example, the APACHE II score) was unavailable and the review of co-morbidity is limited the lack of data on the patient's underlying disease status.

Conclusion

Our research, show that MRSA bacteremia was more likely to be associated with extrinsic factors, such as surgery, two or more invasive devices and two or more antimicrobials than those of MSSA. This study suggests that in patients with *S. aureus* bacteremia, outcome is influenced by age (≥ 60 years old), vancomycin use and primary versus secondary bacteremia. Future investigators of SAB should take into consideration acute severity of illness at onset as well as others factors when evaluating or comparing outcomes.

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