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Major Article

Active surveillance to determine the impact of methicillin resistance on mortality in patients with bacteremia and influences of the use of antibiotics on the development of MRSA infection

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ABSTRACT

Introduction: Methicillin-resistant *Staphylococcus aureus (*MRSA) is among the most important pathogens of nosocomial infections, mainly in intensive care units (ICUs), and accounts for 40-60% of all healthcare-associated *S. aureus* infections. We evaluated the incidence of nosocomial infection by *S. aureus,* identified the risk factors for MRSA infection, and evaluated the effect of resistance to methicillin on mortality in patients. **Methods:** We conducted MRSA surveillance at a university hospital in Brazil from January 1, 2010, to December 31, 2010, and performed a retrospective case-control matched study to evaluate the frequency of subsequent MRSA bacteremia and death among patients. We evaluated and compared the risk factors between patients with MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA) infection. **Results:** Sepsis was the most common cause of infection (17.7/1,000 patient-days), followed by surgical site (11.4/1,000 patient-days), pneumonia (4.1/1,000 patient-days), and urinary tract infection (2.4/1,000 patient-days). The significant risk factors were time of hospitalization, use of central vascular catheter (CVC), urinary catheter, nasogastric tube, parenteral nutrition, tracheostomy, mechanical ventilation, and previous antibiotic administration, the latter of which was the only independent risk factor for MRSA infection. Mortality was significantly higher in patients with MRSA. The number of antibiotics tested was not related to increases in the frequency of MRSA/1,000 patient-days. The incidence of mortality attributable to MRSA (bloodstream infection) BSI was 50%. **Conclusions:** Surveillance results showed that the use of high levels of antibiotics was directly related to the development of MRSA infection, and the mortality attributable to MRSA in patients with bacteremia was significant.

Keywords: Methicillin-resistant *Staphylococcus aureus*. Bloodstream infection. Attributable mortality.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus (*MRSA) is among the most important pathogens of nosocomial infections, mainly in intensive care units (ICUs). MRSA has become endemic in most hospitals worldwide[1,2] and accounts for 40-60% of all healthcare-associated *Staphylococcus aureus* infections[3,4]. The relative morbidity and mortality of nosocomial infection caused by MRSA compared with those associated with methicillin-sensitive *Staphylococcus aureus* (MSSA) remains controversial[5].

In Brazil, the incidence of MRSA is high, particularly in tertiary-care hospitals. In Uberlândia, rates vary from 49.5% among patients hospitalized in general medical clinics to 63.7% among patients in ICUs[6,7].

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Staphylococcus aureus bacteremia is a leading cause of mortality in nosocomial settings; thus, the investigation of bacteremia caused by MRSA has become a major focus of interest over the past few years. Several studies have shown that the characteristics of patients infected with MRSA differed from those of patients with MSSA. Methicillin-resistant *Staphylococcus aureus* bacteremia is associated with a significantly higher mortality rate than MSSA[7,8].

Objective

In the current study, we evaluated the incidence of nosocomial infection by *S. aureus* and identified the risk factors that predispose hospitalized patients to develop MRSA infections. Additionally, we evaluated the effect of methicillin resistance on mortality in patients.

METHODS

Hospital - wide *Staphylococcus aureus* surveillance

We conducted surveillance for MRSA at a university hospital in Brazil from January 1, 2010, to December 31, 2010, using surveillance methods that have previously been described[9].

Briefly, when a new case of MRSA in an inpatient was identified, the workers in the microbiology laboratory of the hospital warned us. We performed standardized data collection of demographic and clinical information from the patients' medical records, including the site of the MRSA acquisition and the clinical indication for the culture that yielded a MRSA diagnosis.

Acquired nosocomial infection was defined according to the Center for Disease Control and Prevention System (CDC)[9]. Infections that were acquired 48h or more after admission to the hospital were classified as hospital-acquired infections.

We defined in-hospital mortality as any death of a patient during the study period. The mortality rate attributable to MRSA bacteremia was the difference between the mortality rate of patients with MRSA (bloodstream infection) BSI and that of patients with MSSA BSI. The Research Ethics Committee of the university approved the study.

Design of the study

This survey was divided into two stages. The first stage entailed a case-control study in the hospital by the National Health-care Safety Network (NHSN) System[9]. Data from patients with MRSA infection were compared with those from patients with MSSA infection to determine risk factors associated with the development of MRSA infection. After the first phase, a retrospective case-control matched study was conducted to evaluate the frequency of subsequent MRSA bacteremia and death among patients newly identified as harboring MRSA. We defined a case as a patient with at least one positive blood culture for MRSA who was treated with glycopeptides and had evidence of sepsis, according to the criteria recommended by the Centers for Disease Control (CDC). The controls were individuals who developed MSSA blood stream infections (BSIs) during the hospital stay. Excluded from this group were patients with positive cultures for MRSA at another anatomic site, patients with no negative blood cultures, and patients treated empirically with vancomycin or fluoroquinolones for a period of more than 24h. We matched the controls based on the following criteria: gender, age difference of no more than 15 years, similar diagnosis upon hospital admission, surgery, difference in dates of admission to the hospital of no more than 2 years, and a difference in the period of hospitalization of less than the number of days between the patient's admission (case) and the emergence of MRSA bacteremia[10].

Risk factors

We evaluated the risk factors for developing MRSA infection by comparing patients with MRSA and MSSA infection.

Ecological study

To calculate the defined daily dose (DDD), we obtained a report of the consumption of antibiotics from the Hospital of Clinics of Federal University of Uberlândia (HC-UFU) pharmacy.

We retrospectively examined the antimicrobial utilization information for all patients using the hospital pharmacy computer database. The evaluated period was from January 1, 2010, to December 31, 2010 (DDDs of antimicrobials were correlated with the monthly incidence of MRSA). The DDD was developed by the World Health Organization (WHO)[11]. We obtained the density of use (DDD per 1,000 patient-days) using the following parameters: DDD, consumption of antibiotics in grams; DDD[12]; DDD/1,000 patient-days = DDD x 1,000; number of patient-days.

Statistical analysis

Proportions were used as the descriptive statistic for categorical and ordinal variables. Differences in the study population were analyzed by the Student's t-test, the Kruskal-Wallis test, Spearman's correlation analysis, the Mantel-Haenzel X^2 test, or Fisher's exact test, as appropriate. The 95% confidence intervals (95% CIs) were computed for each estimate of interest. Data were analyzed using a commercial statistical package, Statistical Package for the Social Sciences (SPSS) PC version 11.0 (SPSS, Chicago) and Epi-Info Software version 2000 (CDC, Atlanta). To test the hypothesis that mortality in patients with MRSA BSI was significantly different from that in controls, we used the McNemar test. A multivariate logistic regression model was fitted to identify independent factors of MRSA infection.

RESULTS

Epidemiological indicators and risk factors associated with MRSA infection

Epidemiological indicators for infection are shown in **Table 1** and revealed an infection rate of 40.5 per 1,000 patient-days. The MSSA infection rate (27.5/1,000 patient-days) was higher than the MRSA infection rate (12.9/1,000 patient-days). Sepsis was the most common cause of infection during the investigated period (17.7/1,000 patient-days), followed by surgical site infection (11.4/1,000 patient-days), pneumonia (4.1/1,000 patient-days), and urinary tract infection (2.4/1,000 patient-days).

Among the patients with MRSA, the variables identified by univariate analysis as significant risk factors associated with the development of infection were as follows: time of hospitalization ($p<0.0001$); use of a central venous catheter (CVC) ($p<0.0001$); use of a urinary catheter ($p=0.0001$); nasogastric tube ($p=0.001$); parenteral nutrition ($p=0.001$); tracheostomy ($p=0.004$); mechanical ventilation ($p=0.002$); and previous antibiotic administration ($p<0.0001$). In the multivariate analysis, only previous antibiotic administration was an independent risk factor for the development of MRSA infection. The mortality rate was significantly higher in patients with MRSA **(Table 2)**.

Defined daily dose of antibiotics and MRSA infection

Most (70.4%) patients used an antibiotic during hospitalization, and approximately 70% of these patients used more than two antibiotics. Consumption data on 3rd and 4th generation cephalosporins, carbapenems, and vancomycin in DDD per 1,000 patient-days are shown in **Table 3**. The consumption of these antibiotics during the investigated period

TABLE 1 - Rates of *Staphylococcus aureus* infection in patients hospitalized in Hospital of Clinics of Federal University of Uberlândia, State of Minas Gerais, Brazil, between January and December 2010.

Epidemiological indicators	Rates
Staphylococcus aureus infection/1,000 patient-days	40.5
Staphylococcus aureus sepsis/1,000 patient-days	17.7
Staphylococcus aureus pneumonia/1,000 patient-days	4.1
Staphylococcus aureus surgical site infection/1,000 patient-days	11.4
Staphylococcus aureus urinary tract infection/1,000 patient-days	2.4
MRSA infection/1,000 patient-days	12.9
MSSA infection/1,000 patient-days	27.5

MRSA: methicillin-resistant *Staphylococcus aureus;* MSSA: methicillin-sensitive *Staphylococcus aureus*.

TABLE 2 - Univariate analysis of risk factors for the acquisition of methicillin-resistant *Staphylococcus aureus* infection.

Variables	MRSA n=61 (%)	MSSA n=169 (%)	P > 0.05*	OR (CI)
Gender				
male	38 (62.2)	95 (56.2)	0.50	1.29 (0.68-2.45)
Age (average/SD)	48,3 (21.9)	39,1 (25.6)	0.01	-
Hospitalization (average/SD)	43,2 (44.5)	20,5 (23.9)	<0.0001	-
Surgery	23 (37.8)	63 (37.3)	0.92	1.02 (0.53-1.94)
Comorbidities				
cancer	8 (13.1)	19 (11.2)	0.87	1.19 (0.45-3.09)
heart disease	9 (14.8)	13 (7.7)	0.17	2.08 (0.77-5.57)
nephopathy	9 (14.8)	11 (6.5)	0.09	2.49 (0.89-6.92)
diabetes mellitus	11 (18.0)	19 (11.2)	0.25	1.74 (0.72-4.17)
others**	9 (14.8)	29 (17.2)	0.81	0.84 (0.34-2.00)
Invasive devices				
central venous catheter	26 (42.6)	33 (19.5)	<0.0001	3.06 (1.55-6.06)
urinary catheter	22 (36.1)	22 (13.0)	0.0001	3.77 (1.79-7.94)
nasogastric tube	19 (31.1)	20 (11.8)	0.001	3.37 (1.55-7.32)
parenteral nutrition	3 (4.9)	8 (4.7)	0.001	3.37 (1.55-7.32)
tracheostomy	7 (11.5)	3 (1.8)	0.004	7.17 (1.60-36.44)
drain	2 (3.3)	3 (1.8)	0.61	1.88 (0.21-14.23)
mechanical ventilation	18 (29.5)	19 (11.2)	0.002	3.22 (1.46-7.09)
Use of antibiotics				
previous	32 (52.4)	27 (15.9)	<0.0001	5.80 (2.89-11.73)

MRSA: *methicillin-resistant Staphylococcus aureus*; MSSA: *methicillin-sensitive Staphylococcus aureus;* OR: odds ratio; CI: confidence interval; SD: standard deviation; *Fisher exact test and Student´s t test; **Polytrauma, COPD (chronic obstructive pulmonary disease), cholelithiasis, dyslipidemia, lupus, Parkinson's, HIV (human immunodeficiency virus), venous insufficiency, pancreatic insufficiency, cystic fibrosis, obesity, hepatitis, pulmonary emphysema, congenital toxoplasmosis, arthritis.

TABLE 3 - Success of matched variables of patients with bloodstream infection by methicillin-resistant *Staphylococcus aureus*, cases and their controls, in the Hospital of Clinics of Federal University of Uberlândia, State of Minas Gerais, Brazil*.

Variables	Total of pairs (N)	Reached number pairs	Success percentage achieved
Difference in age not exceeding 15 years	14	10	71.4
Gender	14	12	85.7
Admission date	14	14	100.0
Similar hospitalization	14	10	71.4
Similar admission diagnosis	14	11	78.6
Similar surgical procedure	04	2	50.0
Total	74	59	79.7

varied, however; the use of extended-spectrum cephalosporins, averaging 113.5 DDD per 1,000 patient-days, was higher than the use of vancomycin (38.7 DDD per 1,000 patient-days) and carbapenems (25.8 DDD per 1,000 patient-days), but the use of cephalosporins was not related to the increased incidence of MRSA nosocomial infection/1,000 patient-days in the period from July to December 2010. The large number of antibiotics tested was not related to the increase in the frequency of MRSA/1,000 patient-days in the *Hospital de Clínicas da Universidade Federal de Uberlândia* (HC-UFU) **(Figure 1)**.

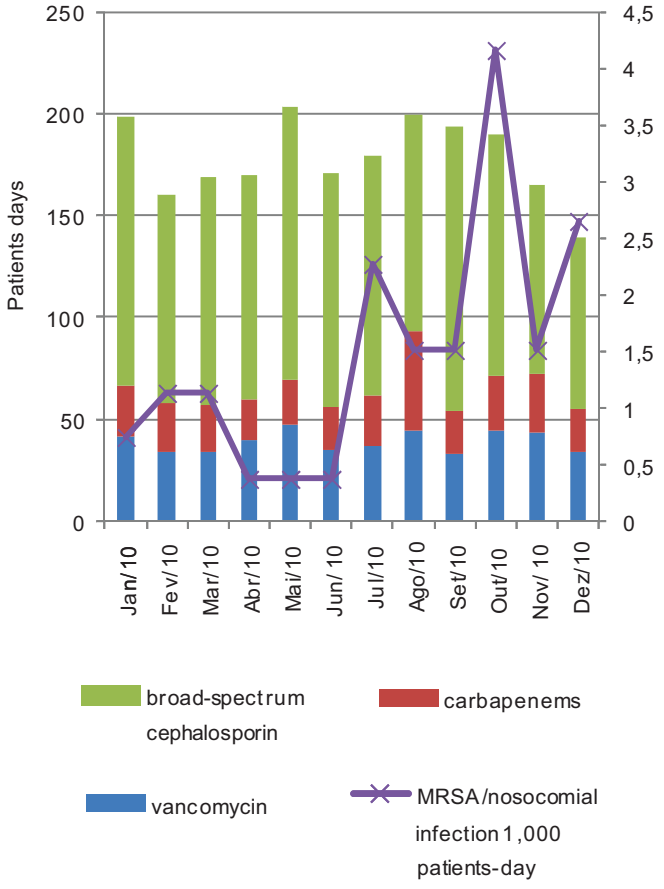

FIGURE 1 - Rates of methicillin-resistant *Staphylococcus aureus* nosocomial infections per 1,000 patient-days and defined daily doses of antibiotics used by patients hospitalized between January and December 2010 (data were analyzed by Spearman correlation analysis). MRSA: Methicillin-resistant *Staphylococcus aureus*

Attributable mortality

Thirty of the 45 patients in the cohort died in the hospital (case fatality rate = 66.7%). Mortality rates were similar between the 2 groups of patients; specifically, 10 (66.7%) of the patients with MRSA bacteremia died, compared with 20 (66.7%) of the patients with MSSA bacteremia (p=0.67). An analysis of patients whose deaths were directly or likely attributable to *S. aureus* bacteremia showed a statistically significant association between the presence of methicillin resistance and increased mortality. We determined the mortality attributable to MRSA by matching cases and controls, based on a selection of 14 patients in the control group. The success rate of variables used to match cases and controls was 80%, and the variable *date of admission* had a successful matching rate of 100% **(Table 3)**. The mortality rate in the case group was 71.4% (10/14 cases), while 3 of the controls died, corresponding to a mortality rate of 21.4%; therefore, the mortality rate attributable to MRSA BSI was 50% (p=0.0134) **(Table 4)**.

TABLE 4 - Mortality of 14 pairs of patients, with bloodstream infection caused by methicillin-resistant *Staphylococcus aureus* and their respective controls in the Hospital of Clinics of Federal University of Uberlândia, State of Minas Gerais, Brazil*.

	Controls		
Cases	died	survived	total
Died	3	7	10
Survived	0	4	4
Total	3	11	14

*McNemar test

DISCUSSION

This study is one of the few studies in the literature that investigates mortality attributable to nosocomial MRSA infections. According to the literature, MRSA infections have a high prevalence in larger hospitals because of the presence of patients with more risk factors, including advanced age, high illness severity, lengthy hospitalization, use of invasive devices (particularly a central vascular catheter - CVC), mechanical ventilation, urethral catheterization, use of antibiotics, and disability practices for prevention and control of nosocomial infections[13-15].

In the present study, more than 90% of the risk factors were associated with MRSA infection. The univariate analysis revealed several factors associated with an increased risk of acquiring MRSA infection, including length of hospital stay, use of a CVC, urinary catheter, nasogastric tube, parenteral nutrition, tracheostomy, mechanical ventilation, and previous antibiotic use. Only the previous use of antibiotics was an independent risk factor for acquiring MRSA infection.

Among the factors that contributed to a causal association between antibiotic use and bacterial resistance, the time and intensity of exposure to antimicrobials was the most significant[16]. This factor is evident in critical care units, where patients are subjected to a few intense antibiotic regimens and there is a greater frequency of multi-drug-resistant microorganisms[16,17]. In our study, we performed an assessment of DDD in clinics where cases of infection were detected, and we were unable to demonstrate this relationship; however, the DDDs in our hospital were similar to those reported in other studies involving tertiary hospitals[18]. When this evaluation was performed in other critical care units, the use of these drugs was found to be much higher than that in North American and European ICUs, especially with respect to extended-spectrum cephalosporins and carbapenems (data not shown)[12,19]. Data not shown.

The high proportion of *S. aureus* nosocomial bacteremia caused by methicillin-resistant strains indicates the importance of this organism as a significant cause of this infection in hospitals[3]. The evidence indicates that bacteremia caused by MRSA is associated with higher morbidity and mortality rates than that associated with MSSA[7,8], but there is no conclusive evidence that the isolates of MRSA are more virulent than those of MSSA[21,22]. Although the mortality associated with MRSA infections is considered to be higher than that associated with MSSA infections, the data are controversial, especially considering that the mortality associated with MSSA BSI is also likely significant. The mortality and morbidity rates in the literature differ significantly from our rates, which can be explained by methodological issues, including the choice of variables used for matching[23,24].

There are some difficulties associated with matching patients in matched case-control studies, and, as previously mentioned, MRSA nosocomial infections are usually associated with risk factors such as advanced age, complications related to diagnostic and therapeutic procedures, and several co-morbidities[25], which characterize patients as more susceptible to acquiring these infections and make it more difficult to pair controls. In our study, only one child was infected with MRSA who was not matched to a control, allowing the evaluation of the remaining 93.3% of the population with BSI. Among the 74 variables applied in the matching of cases and controls, 59 (80%) were successfully used.

The results obtained in our study showed a mortality rate of 71.4% in cases and 21.4% in controls. The mortality rate associated with MRSA BSI was 50%, similar to that reported by Moreira et al.[20] in a university hospital in São Paulo (45.1%).

There are a number of important observations regarding the epidemiological profile of MRSA bacteremia in our region[26]. MRSA was responsible for a 33.3% rate of BSI caused by *S. aureus* in our hospital. This finding has important implications for empirical antimicrobial therapy in patients with suspected *S. aureus* infections. We attempted to approximate the maximum similarity between cases and controls, which led to the conclusion that those cases and controls in our study were similar in most important respects.

This study has some limitations. First, we had a relatively small number of patients in the case group, thus reducing the statistical power and ability to study subsets of patients. Second, because all our study patients were hospitalized in a single tertiary hospital, our results may not be generalizable to other institutions.

Surveillance results showed that the high use of antibiotics in our hospital was directly related to the development of MRSA infection. The results of our study indicate that the mortality attributable to MRSA in patients with bacteremia was significant. The study therefore provides the background for future investigations of the impacts of antimicrobial resistance and infection control programs for endemic pathogens such as MRSA.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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