NASOPHARYNGEAL COLONIZATION WITH METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS AND MORTALITY AMONG PATIENTS IN AN INTENSIVE CARE UNIT

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Nasopharyngeal colonization with Methicillin-resistant Staphylococcus aureus (MRSA) is common in critically ill patients, but its effect on patient prognosis is not fully elucidated. A retrospective cohort study was carried out enrolling 122 patients from an intensive care unit who were screened weekly for nasopharyngeal colonization with MRSA. The outcomes of interest were: general mortality and mortality by infection. Several exposure variables (severity of illness, procedures, intercurrences and MRSA nasopharyngeal colonization) were analyzed through univariate and multivariable models. Factors significantly associated with mortality in general or due to infection were: APACHE II and lung disease. The performance of surgery predicted favorable outcomes. MRSA colonization did not predict mortality in general (OR=1.02; 95%CI=0.35-3.00; p=0.97) or by infectious causes (OR=0.96; 95%CI=0.33-2.89; p=0.96). The results suggest that, in the absence of severity of illness factors, colonization with MRSA is not associated with unfavorable outcomes.

DESCRIPTORS: Staphylococcus aureus; intensive care units; mortality

COLONIZACIÓN NASAL POR EL STAPHYLOCOCCUS AUREUS RESISTENTE A LA METICILINA Y MORTALIDAD EN PACIENTES DE UNA UNIDAD DE TERAPIA INTENSIVA

La colonización nasofaríngea por el Staphylococcus aureus resistente a la meticilina (Methicillin-resistant S.aureus - MRSA) es común en pacientes críticamente enfermos, pero su efecto sobre el pronóstico no está completamente esclarecido. Fue realizado un estudio de Cohorte retrospectivo con 122 pacientes de una Unidad de Terapia Intensiva que realiza semanalmente exámenes para constatar la colonización nasofaríngea por MRSA. Lo encontrado de interés fue: mortalidad general y mortalidad por causas infecciosas. Diversas variables de exposición (gravedad, procedimientos ocurrencias y colonización nasofaríngea por MRSA) fueran analizadas en modelos univariados y multivariados. Los factores asociados significativamente a la mortalidad en general o por causas infecciosas fueran: APACHE II y enfermedad pulmonar. La realización de cirugía predijo mejor el pronóstico. La colonización por MRSA no predijo la mortalidad en general (OR=1.02; IC95%=0.35-3.00; p=0.97) o por causas infecciosas (OR=0.96; IC95%=0.33-2.89; p=0.96). Los resultados sugieren que, en la ausencia de factores de gravedad, la colonización por MRSA no se asocia al peor pronóstico.

DESCRIPTORES: Staphylococcus aureus; unidades de terapia intensiva; mortalidad

COLONIZAÇÃO NASAL POR STAPHYLOCOCCUS AUREUS RESISTENTE À METICILINA E MORTALIDADE EM PACIENTES DE UMA UNIDADE DE TERAPIA INTENSIVA

A colonização de nasofaringe por Staphylococcus aureus, resistente à meticilina (Methicillin-resistant S.aureus - MRSA), é comum em pacientes criticamente doentes, mas seu significado prognóstico não é inteiramente conhecido. Realizou-se estudo de coorte retrospectivo com 122 pacientes de uma unidade de terapia intensiva que realizaram triagem semanal para colonização por MRSA. Os desfechos de interesse foram: mortalidade geral e mortalidade por infecção. Diversas variáveis de exposição (gravidade, procedimentos, intercorrências e colonização nasofaríngea por MRSA) foram analisadas em modelos univariados e multivariados. Fatores significativamente associados à mortalidade geral ou por infecção foram: APACHE II e doença pulmonar. A colonização por MRSA não foi preditora de mortalidade geral (OR=1,02; IC95%=0,35-3; p=0,97) ou por infecção (OR=0,96; IC95%=0,33-2,89; p=0,96). Os resultados sugerem que, na ausência de fatores de gravidade, a colonização por MRSA não caracteriza pior prognóstico.

DESCRITORES: Staphylococcus aureus; unidades de terapia intensiva; mortalidade

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INTRODUCTION

Hospital-acquired infections (HAI) are among the main adverse occurrences related to the care of patients in Intensive Care Units (ICUs)[1]. A predominance of multidrug-resistant (MDR) microorganisms has been shown in the etiology of these infections[2] in several countries, including Brazil. MDR microorganisms are defined as those that are resistant to one or more classes of antimicrobials routinely used in their treatments[3]. The *methicillin-resistant staphylococcus aureus* (MRSA) stands out among them. This bacterium was first described in Europe in 1961 and was globally disseminated in following decades[4]. Strains of MRSA are resistant to all beta-lactam drugs (penicillins, cephalosporins and carbapenems) and several other classes of antimicrobials (clindamycin, quinolones)[5].

Data from the National Nosocomial Infection Surveillance System (NNIS) in the United States reveal that MRSA corresponded to 59.5% of *S.aureus* strains isolated from ICUs[6]. Brazilian data point to a similar scenario. A report from the Epidemiological Surveillance Center of the state of Sao Paulo has identified *S.aureus* as the second most frequent bacterium found in blood cultures collected in ICUs, corresponding to 26.7% of positive exams; among the isolated strains, 58.8% were MRSA[7].

Nasopharyngeal colonization generally precedes the emergence of infection by MRSA. In addition, colonized patients can spread this agent in ICUs, contributing to increased morbidity and mortality[8]. The identification and isolation of individuals infected by MRSA, even when these do not present signs of active infection, contribute to reduce the circulation of this agent and also its participation in the HAI etiology. A common practice used to identify colonized individuals is the performance of "active surveillance cultures"[9], a periodic collection of cultures of nasopharyngeal secretions using swabs.

Although the epidemiological utility of surveillance cultures has been proven, the impact of nasal colonization in patients' prognosis has not been established[9]. This study's objective was twofold: to analyze the effect of MRSA colonization on the prognosis of patients hospitalized in Intensive Care Units and to identify other predictors of mortality for the patients of this study.

METHOD

Study site

This study was carried out in the Adults' Intensive Care Unit (AICU) of the Bauru State Hospital (BSH). This is a teaching hospital linked to Botucatu School of Medicine, Sao Paulo State University (UNESP). The hospital currently has 280 beds in use and four ICUs. The AICU has 11 beds and cares for medical and surgical patients.

Study Design

This is a retrospective cohort study, enrolling 122 patients admitted to the AICU between May 2005 and March 2006. These patients were screened for MRSA through surveillance cultures (nasopharyngeal swabs) at the time of their admission and weekly during their hospitalization. Procedures for microbiological analysis and antimicrobial susceptibility tests followed standards recommended by the literature[10]. Two outcomes were considered: (1) death and (2) death caused by or related to infection.

The following variables were studied: (1) demographic data; (2) comorbidities and severity of illness at the time of admission; (3) invasive procedures, devices and use of imunossupressive medication; (4) HAI diagnosis; (5) MRSA colonization. These data were evaluated in relation to the overall chance of dying (Study 1) and to death caused by/ related to infection (Study 2). The severity of patients' conditions was determined by scores obtained in the Acute Physiology and Chronic Health Evaluation II (APACHE II), computed at the time of admission[11]. Definitions of HAI followed guidelines provided by the Centers for Disease Control and Prevention[12].

Statistical analysis

Data were entered in the EPI INFO v.3.2. (©DC, USA) and analyzed through the SPSS statistical software v.15.0 (©SPSS Inc.).

Univariate analysis

Dichotomous variables were analyzed through the Chi-Square Test or Fischer's Exact Test, when appropriate. Age was evaluated by the Student's T-Test, while APACHE II scores were evaluated through the Mann-Whitney Test.

Multivariable analysis

Variables were included in hierarchical models of logistic regression. The order of introduction was: 1st group – demographic data; 2nd group – comorbidities and severity of illness at the time of admission; 3rd group – invasive procedures, use of devices and immunosuppressive medication; 4th group – HAI diagnosis. A significance level of 0.05 was required for variables to be kept in the models. However, because MSRA colonization was the variable of primary interest in this study, it was forced into all models, even when it did not reach the required statistical significance. The limit used to define significance in the final model was 0.05.

Ethical aspects

This study was approved by the Ethics Committee for Research with human subjects and is included in the project: Risk factors for the acquisition of isolated multiresistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in patients at the Bauru State Hospital.

RESULTS

MRSA colonization was detected through surveillance cultures in thirty of the studied patients. Mortality in the followed cohort was high: 94 deaths (77%), 67 of which were related to or caused by hospital-acquired infection.

In Study 1, which investigated predictors for general mortality, univariate analysis (Table 1) identified age, lung disease, APACHE II, mechanical ventilation, the presence of nasogastric tubes and diagnosis of sepsis as risk factors for death. Surgeries and drains, on the other hand, were associated with a better prognosis. In the multivariable analysis (Table 3), only APACHE II and lung disease were implicated in a higher death risk. The practice of surgery presented a negative association with mortality. MSRA colonization was not associated with a worse outcome (OR=0.76; CI 95%=0.30-1,97; p=0,58).

Table 1 – Mortality risk factors in patients in the Intensive Care Unit at the Bauru State Hospital (univariate analysis)

Risk factors	Death (n=94)	Survival (n=28)	OR (CI95%)	*p*-value
Demographic data				
Male gender	22 (23.4%)	8 (28.6%)	0.76 (0.30-1.97)	0.58
Age (average)	65.2	56.6	-	0.02*
Co-morbidities				
Heart disease	24 (25.5%)	3 (10.7%)	2.86 (0.79-10.22)	0.09
Lung disease	29 (31.2%)	3 (10.7%)	3.78 (1.06-13.52)	0.03*
Renal disease	9 (9.6%)	1 (3.6%)	2.85 (0.35-23.60)	0.28
Hepatic disease	13 (13.8%)	4 (14.3%)	0.96 (0.29-3.23)	0.58
CNS disease	36 (38.3%)	11 (39.3%)	0.96 (0.40-2.28)	0.93
Diabetes mellitus	32 (34%)	7 (25%)	1.54 (0.60-4.03)	0.37
Neoplasia (solid)	8 (8.5%)	2 (7.1%)	1.20 (0.28-6.05)	0.82
AIDS	8 (8.5%)	1 (3.6%)	2.51 (0.30-20.99)	0.38
Trauma	1 (1.1%)	1 (3.6%)	0.29 (0.02-4.80)	0.41
APACHE Ⅱ (median)	24	18	-	0.002*
Procedures, devices, immunity				
Surgeries	11 (11.8%)	10 (35.7%)	0.24 (0.09-0.65)	0.003*
Mechanic ventilation	84 (89.4%)	18 (64.3%)	4.67 (1.69-12.86)	0.002*
Central venous catheter	72 (76.6%)	19 (67.9%)	1.5 (0.61-3.91)	0.35
Urinary catheter	91 (96.8%)	25 (89.3%)	3.64 (0.69-19.15)	0.11
Nasogastric tube	86 (91.5%)	20 (71.4%)	4.30 (1.44-12.84)	0.006*
Parenteral nutrition	7 (7.4%)	1 (3.6%)	2.17 (0.26-18.45)	0.46
Drains	8 (8.5%)	7 (25%)	0.28 (0.09-0.86)	0.02*
Neutropenia	1 (1.1%)	0	-	0.58
Steroids	45 (47.9%)	11 (39.3%)	1.42 (0.60-3.35)	0.42
Hospital-acquired infections				
Pneumonia	38 (40.4%)	8 (28.6%)	1.69 (0.67-4.24)	0.25
Sepsis (bloodstream infection)	22 (23.7%)	0	-	0.004*
Urinary infection	18 (19.1%)	8 (28.6%)	0.59 (0.22-1.56)	0.20
MRSA colonization	22 (23.4%)	8 (28.6%)	0.76 (0.30-1.97)	0.58

Data in number and percentage, except when indicated
*Statistically significant variables
OR=*Odds Ratio*. CNS = Central Nervous System. APACHE=*Acute Physiology and Chronic Health Evaluation* (severity scoring system for patients in ICU). MRSA= *Methicillin-resistant Staphylococcus aureus*

Study 2 (predictors for mortality by infection) identified the same risk factors found in the univariate analysis carried out in Study 1 (Table 2). In the stage of multivariable analysis, APACHE II and lung disease were predictors of a worse prognosis (Table 3). Once again, MSRA colonization was not associated with a higher risk of death caused by or related to infection (OR=0.96; CI95%=0.33-2.89; p=0.96).

Table 2 – Mortality risk factors related to or caused by hospital-acquired infection in patients in the Intensive Care Unit at the Bauru State Hospital (univariate analysis)

Risk factors	Death (n=67)	Survival (n=28)	OR (CI95%)	*p*-value
Demographic data				
Male gender	41 (61.2%)	16 (57.1%)	1.18 (0.48-2.90)	0.71
Age (average)	65.6	56.6	-	0.02*
Co-morbidities				
Heart disease	16 (23.9%)	3 (10.7%)	2.61 (0.70-9.81)	0.14
Lung disease	21 (31.8%)	3 (10.7%)	3.89 (1.05-14.34)	0.03*
Renal disease	6 (9%)	1 (3.6%)	2.05 (0.31-23.14)	0.67
Liver disease	7 (10.4%)	4 (14.3%)	0.70 (0.19-2.61)	0.73
CNS disease	23 (34.3%)	11 (39.3%)	0.81 (0.33-2.01)	0.65
Diabetes mellitus	28 (41.8%)	7 (25%)	2.15 (0.81-5.76)	0.12
Neoplasia (solid)	6 (9%)	2 (7.1%)	1.28 (0.24-6.76)	1.00
AIDS	5 (7.5%)	1 (3.6%)	2.18 (0.24-19.54)	0.67
Trauma	0	1 (3.6%)	-	0.30
APACHE II (median)	24	18		<0.001
Procedures, devices, immunity				
Surgeries	10 (15.2%)	10 (35.7%)	0.32 (0.12-0.90)	0.03*
Mechanic ventilation	61 (61%)	18 (64.3%)	5.65 (1.81-17.67)	0.005
Central venous catheter	51 (76.1%)	19 (67.9%)	1.51 (0.57-3.99)	0.40
Urinary catheter	67 (100%)	25 (89.3%)	-	0.02*
Nasogastric tube	62 (92.5%)	20 (71.4%)	4.96 (1.46-16.90)	0.02*
Parenteral nutrition	7 (10.4%)	1 (3.6%)	3.15 (0.37-26.88)	0.43
Drains	8 (11.9%)	7 (25%)	0.41 (0.13-1.26)	0.13
Neutropenia	0	0	-	-
Steroids	35 (52.2%)	11 (39.3%)	1.69 (0.69-4.15)	0.25
Hospital-acquired infections				
Pneumonia	31 (46.3%)	8 (28.6%)	2.15 (0.83-5.57)	0.11
Sepsis (bloodstream infection)	21 (31.8%)	0	-	0.001*
Urinary infection	16 (23.9%)	8 (28.6%)	0.78 (0.29-2.12)	0.63
MRSA colonization	17 (25.4%)	8 (28.6%)	0.85 (0.32-2.28)	0.75

*Statistically significant variables
OR=*odds ratio.* CNS = Central Nervous System. APACHE=*Acute Physiology and Chronic Health Evaluation* (severity scoring system for patients in ICU)
MRSA= *Methicillin-resistant Staphylococcus aureus*

Table 3 – Multivariable analysis of risk factors related to general mortality and mortality related to or caused by hospital-acquired infection in patients in the Intensive Care Unit at the Bauru State Hospital

Risk Factors	OR (CI95%)	p-value
General mortality		
APACHE II	1.10 (1.04-1.18)	0.003
Lung disease	5.72 (1.37-23.93)	0.02
Surgery	0.42 (0.11-0.95)	0.04
MRSA colonization	1.02 (0.35-3.00)	0.97
Mortality due to infection		
APACHE II	1.11 (1.04-1.19)	0.002
Lung disease	6.02 (1.43-25.46)	0.02
MRSA colonization	0.96 (0.33-2.89)	0.96

OR=*odds ratio.* APACHE=*Acute Physiology and Chronic Health Evaluation* (severity scoring system for patients in ICU). MRSA= *Methicillin-resistant Staphylococcus aureus*

DISCUSSION

Infection control practices should be seen as an important part of a larger context: the promotion of quality and safe care to patients[13]. That is why a critical evaluation of risks related to healthcare is essential and applies to the control of MDR microorganisms. This study aims to contribute to a better understanding of the risks posed by the acquisition of MRSA in critical patients.

Some recent studies evaluated mortality due to MSRA in hospitalized patients. The majority involved patients with blood cultures positive for MRSA (bacteremia). One of these studies carried out in a

Brazilian teaching hospital compared mortality in patients with cultures positive for MSRA and for methicillin-susceptible S.aureus (MSSA). The authors concluded that the risk was higher for patients affected by MRSA[14]. One study from the United States, on the other hand, compared similar groups, carefully matching cases according to the severity of illness[15] and their results did not find differences in mortality between MRSA and MSSA patients. Patients with MRSA, though, were hospitalized for longer periods and incurred higher costs for the hospital. Other studies addressing patients with bacteremia obtained conflicting results[16-17].

Studies that follow cohorts of patients colonized by MRSA are rarer. The follow up of transplanted patients and/or patients awaiting for hepatic transplantation revealed that nasal carriage increased the risk of infection by 15 fold but had no impact on mortality[18]. In another study, authors followed individuals chronically infected by MRSA[19] and, of the 281 persistent carriers, 96 presented infections and 14 died.

In the casuistic of this study, asymptomatic carriage of MRSA did not increase the risk of general mortality nor of mortality caused by infection. Instead, the usual mortality predictors in patients in ICUs were identified. The APACHE II is a scoring system that has the precise function of predicting death risk. Therefore, its statistical significance is not surprising. The presence of lung disease increases the need for ventilatory support and the risk of hospital-acquired pneumonia. Surgical patients, on the other hand, are known to be the group with the best prognosis[11].

Although these findings are interesting, they should be interpreted with caution. The fact that MRSA colonization by itself does not determine death does not mean that infections by this agent are associated with a good prognosis. One should take into account that mortality in the studied cohort was very high (77%). In other words, MRSA colonization did not increase the risk of death in a group of severely ill patients. What would have been the results if we had studied individuals whose primary diseases had a better prognosis? Further research is needed to answer this question.

Another question arises. Will the results of this study be used as a rationale against the need for active surveillance cultures? It is a fact that the collection of these cultures increases laboratorial costs and the workload of professionals from infection control committees[8-9]. However, we believe that a conclusive answer for the real need for surveillance cultures requires clarification of other factors. Among them, the impact of MRSA colonization on the incidence of infections, patients' length of stay at the hospital and hospital costs. This is an open field for research.

We know that MRSA is an important agent of HAIs in ICUs. A rigid implementation of protocols to prevent HAIs, isolation precautions and hand hygiene is recommended for its control. Intervention studies have shown that increased adherence to these measures reduces HAI and mortality rates[20]. This is a challenge for health professionals, on whose hands lay (literally) the responsibility for controlling infections.

We conclude that MRSA colonization in the studied population was not associated with higher mortality rates. Other studies – focusing on morbidity indicators and hospital costs – are necessary to better assess the impact of this agent in patients admitted to ICUs.

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