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ORIGINAL ARTICLE

Risk factors for methicillin-resistant *Staphylococcus aureus* bacteremia: A multicenter matched case-control study

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Introduction: Methicillin-resistant *Staphylococcus aureus* is a frequent pathogen at critical care services. Its presence leads to increased hospital stays and mortality risk in patients with bacteremia. However, the etiology of this resistance marker has not been fully studied.
Objective: To identify risk factors associated with the emergence of methicillin-resistant *S. aureus* bacteremia in critically ill patients treated at intensive care units in Bogotá, Colombia.
Materials and methods: We conducted a retrospective paired case-control study, nested in a cohort of patients diagnosed with *S. aureus* bacteremia and treated at intensive care units between 2006 and 2008 in Bogotá. Cases were patients with positive blood culture to methicillin resistance, matched in a 1:1 ratio with methicillin-sensitive controls isolated from the same institution and hospitalization year. We used conditional logistic regression to analyze the risk factors associated with the presence of resistance, with emphasis on prior antibiotic therapy.
Results: We included 372 patients with *S. aureus* bacteremia. Factors such as the use of pre-hospital devices: vascular (OR=1.986, 95% CI 1.038 to 3.801) and urinary (OR=2.559, 95% CI: 1.170 to 5.596), along with the number of previously used antibiotics, were associated with the emergence of resistance. The number of antibiotics used previously was determined to have a gradient effect, particularly carbapenems.
Conclusions: The rational use of antibiotics and surveillance of exposure to surgical procedures or use of invasive devices are interventions that could diminish the emergence of methicillin-resistant *S. aureus* bacteremia causes.

Key words: Methicillin-resistant *Staphylococcus aureus*; risk factors; drug resistance, microbial; intensive care units; case-control studies.

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Factores de riesgo de la resistencia a meticilina de *Staphylococcus aureus* causante de bacteriemia: estudio multicéntrico de casos y controles emparejados

Introducción. *Staphylococcus aureus* resistente a la meticilina es uno de los agentes patógenos más frecuentes en las unidades de cuidados intensivos. Su presencia prolonga las hospitalizaciones y aumenta el riesgo de mortalidad en los pacientes con bacteriemia. Sin embargo, la etiología de este marcador de resistencia no ha sido completamente estudiada.
Objetivo. Determinar los factores asociados con la aparición de *S. aureus* resistente a la meticilina causante de bacteriemia en pacientes atendidos en unidades de cuidados intensivos en Bogotá.
Materiales y métodos. Se hizo un estudio retrospectivo de casos y controles emparejados, anidado en una cohorte de pacientes con diagnóstico de bacteriemia por *S. aureus* atendidos en unidades de cuidados intensivos de Bogotá entre 2006 y 2008. Los casos fueron pacientes con hemocultivo positivo para resistencia a la meticilina, emparejados 1 a 1 con controles con hemocultivos sensibles

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Juan Sebastián Castillo, Aura Lucía Leal, Jorge Alberto Cortés, Carlos Arturo Álvarez: project design, funding, management and field work implementation
Paola Mariana Arias-Ortiz, Libia del Pilar Calderón, Juan Sebastián Castillo, José Moreno: data review and analysis
All authors participated in manuscript preparation, revision and submission.

a la meticilina de la misma institución y año de hospitalización. Se analizaron mediante regresión logística condicional los factores de riesgo asociados con la presencia de resistencia, con énfasis en el tratamiento previo con antibióticos.

Resultados. Se incluyeron 372 pacientes con bacteriemia por *S. aureus*. Factores como el uso de dispositivos previos a la hospitalización: vasculares (*Odds ratio*, OR=1,986; $IC_{95\%}$ 1,038-3,801) y urinarios (OR=2,559; $IC_{95\%}$ 1,170-5,596), así como el número de antibióticos administrado previamente, se asociaron con la aparición de resistencia. Se registró un efecto de gradiente con el número de antibióticos usados previamente, especialmente carbapenémicos.

Conclusiones. El uso racional de antibióticos y la vigilancia de la exposición a procedimientos quirúrgicos o al uso de dispositivos invasivos, son intervenciones que podrían disminuir la aparición de *S. aureus* resistente a meticilina causante de bacteriemia.

Palabras clave: *Staphylococcus aureus* resistente a meticilina; factores de riesgo; farmacorresistencia microbiana; unidades de cuidados intensivos; estudios de casos y controles.

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The emergence of resistant microorganisms is a worldwide phenomenon with serious implications on the quality of care and the efficiency of health services (1). Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the principal microorganisms that cause infections in hospitals, especially in intensive care units (ICU). Bloodstream infections are notable among those caused by this agent (2). Methicillin resistance has been shown to impact clinical and economic outcomes negatively, particularly in terms of increased morbimortality and duration of hospitalization, as well as the demand for additional interventions to mitigate its clinical impact (3,4). The emergence of MRSA in the ICU is a priority problem because of the convergence of factors in critically ill patients such as the existence of comorbidities involving immune response effects, intensive use of devices and antibiotics and the circulation of resistant strains (5). To reduce the effect of the infection, studies have recommended anticipating the diagnosis of methicillin-resistant *S. aureus* and administering appropriate and timely therapy (6,7).

In order to classify patients who could become infected with MRSA, proven risk factors must be evaluated in advance to compensate for the current limitations in determining an early diagnosis (6). MRSA bacteremia emergence among ICU patients has been associated with several factors, which can be classified according to three groups: a) those related to the microorganisms, primarily the spread of resistant clones (8); b) those associated with the host, which include age, sex, presence of comorbidities (particularly chronic illnesses), previous use of antibiotics and invasive devices (9-12), and c) the characteristics of hospital and community environments (9,11,13), particularly previous use of antibiotics given the high risk associated with this factor and the control of cross-transmission of microorganisms.

In Colombia, the rates of resistance to methicillin in *S. aureus* bacteremia are roughly 33% of all isolates. In spite of a decreasing trend in MRSA, both mortality as well as negative outcomes for the health system continue to be of concern (14). The early identification of patients with MRSA bacteremia and interventions to prevent risk factors related to its emergence can contribute to mitigating the phenomenon. Nevertheless, no studies exist in Colombia that adequately identify the factors associated with the emergence of methicillin resistance in patients with bloodstream infections treated in intensive care units. Therefore, the present study, conducted in a hospital network in the city of Bogotá, Colombia, determined the factors associated with the emergence of MRSA as a causal agent of bacteremia in critically ill patients treated at the ICU.

Materials and methods

Design and participants

This was a case-control study of patients diagnosed with *S. aureus* bacteremia selected from 41 intensive care units at 18 public and highly complex hospitals in Bogotá between January 2006 and December 2008. Cases were defined as patients over 15 years of age hospitalized in the ICU with methicillin-resistant *S. aureus* bacteremia confirmed by blood culture according to the criteria established by infection surveillance systems used in Colombia

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(15). Methicillin resistance was determined using the automated systems VITEK® (bioMérieux Inc., Marcy l'Étoile, France) and MicroScan® (Siemens Healthcare Diagnostics Inc; Tarrytown, New York, United States). We selected controls among patients with methicillin-susceptible *S. aureus* bacteremia (MSSA) in the institution where each case was diagnosed during the same year of hospitalization. The relationship between cases and controls was 1:1. We excluded patients with polymicrobial bacteremia and those for whom a legible clinical chart was unavailable, or who had previously been included in the study (second isolate).

Definition and recording of variables

A medical team trained in using standardized tools to record information collected demographic and clinical information from the medical record of each individual. Questions and discrepancies in the recording of the information were resolved in a committee composed of infection control professionals at each institution.

We defined use of antibiotics prior to hospitalization as exposure to intravenous antibiotics three months before the bacteremia of interest, and the use of invasive devices as reported clinical history of their use prior to hospitalization or while hospitalized prior to admittance to the ICU. We classified devices as central vascular (central venous catheter, transcutaneous pacemaker, prosthetic valve, endovascular catheter, artery vein fistula and acute dialysis catheter); respiratory (endotracheal tube, thoracostomy tube, mediastinal tube, pleural catheter and tracheotomy cannula); urinary (gall bladder catheter, cystostomy and nephrostomy catheter); gastrointestinal (prosthesis, biliary catheter, peritoneal catheter, nasogastric, orogastric and nasojejunal tubes, gastrostomy, ileostomy and colostomy), and other devices (central nervous system catheter, orthopedic devices and drainages).

We defined "history of surgery" as a report of at least one major surgical procedure within 30 days prior to the blood culture with which the bacteremia was diagnosed, or report of surgery within the previous 12 months in the case of prosthetic implant material, and "history of ICU stay" as a clinical history of at least one day of hospitalization in an ICU unit prior to the bacteremia and up to 6 weeks prior to admittance to the hospital.

Comorbidities were obtained by disaggregating the Charlson's index (16), which includes: Peripheral vascular disease, peptic ulcer, connective tissue disease, hepatic disease, AIDS, hemiplegia and dementia. The cancer category was disaggregated by patients with hematological tumors, solid tumors with metastasis and solid tumors without metastasis. Any patient with the following history was considered immunosuppressed: Use of corticoids over 20 mg per day for more than 15 days, chemotherapy during the six previous months, history of transplants, severe malnutrition or albumin <2.5 mg/dl, uncontrolled diabetes mellitus, organ failure (cirrhosis of the liver or renal insufficiency), neoplasm, HIV infection, autoimmune disease, severe burn and primary genetic immune deficiency disorder.

The primary infection site was defined as the likely location of the origin of the bacteremia according to the treating physician. This was classified based on the criteria described by Calandra, *et al.* (17), for infections in the ICU and Horan, *et al.* criteria (CDC) as: Vascular, respiratory, skin and soft tissues, and others, which included those less frequent (urinary, gastrointestinal, central nervous system, orthopedic and mediastinal origins) (15).

Statistical analysis

We described quantitative variables using central tendencies and dispersions and qualitative variables with absolute and relative frequencies based on the profile of susceptibility to *S. aureus*. The association between risk factors and the emergence of resistance was evaluated with crude and adjusted estimations using conditional logistic regression (18,19), based on the pairing conducted at each institution. To construct the adjusted model, we selected variables reported in the literature and progressively eliminated them using the backward stepwise technique. To evaluate the association between type of previous antibiotic use and methicillin resistance, we adjusted individual models for each group of antibiotics: Beta-lactams, non-carbapenems, carbapenems, quinolone, aminoglycosides and vancomycin. For each case, the final models only included variables with a significance level of $p \leq 0.05$. All the analyses were performed with the Stata version 12 statistical package (20). The figures were designed with GraphPad®, Version 6.05 (Trial) (GraphPad Software, Inc. La Jolla, CA, USA) (21).

Results

We included 372 subjects in the study, 186 cases of MRSA bacteremia, and 186 MSSA bacteremia paired by institution and year.

Table 1 summarizes the distribution of the baseline characteristics and differences among groups. No statistically significant differences were observed among groups in terms of sex (p=0.250), age (p=0.918), comorbidities (p=0.340), immunosuppression (p=0.34), history of previous hospitalization (p=0.31), previous stay in the ICU (p=0.21), primary infection site (p=0.56) or known source of infection (p=0.69). Although no significant differences were found in history of invasive devices prior to hospitalization (p=0.36), some differences were observed among the subgroups corresponding to type of device.

We demonstrated significant differences between MRSA and MSSA with regard to history of previous surgery (67.2% vs. 39.2%), use of devices prior to hospitalization (94.6% vs. 84.9%), history of previous intravenous antibiotic use (76.9% vs. 30.6%) and place where the bacteremia was acquired.

The multivariate analysis (Table 2) demonstrated an association between the presence of MRSA and history of use of vascular catheters (OR=1.986; 95% CI: 1.038-3.801) and of urinary catheters prior to hospitalization (OR=2.559; 95% CI: 1.170-5.596).The previous use of intravenous antibiotics was also associated with the emergence of methicillin resistance. In addition, a gradient related to the number of antibiotic families used was found in the study population: One family (OR=4.565; 95% CI: 2.541-8.203), two families (OR=12.405; 95% CI: 5.286-29.111) and three or more families (OR=31.742; 95% CI: 8.967-112.367).

The effect of the type of antibiotic, adjusted by history of previous surgery and presence of urinary, respiratory and vascular catheters is summarized in figure 1. We found that the effect of carbapenems on the emergence of MRSA was greater than that of quinolone, beta-lactams, aminoglycosides and vancomycin.

Discussion

Previous intensive exposure to antibiotics emerged as the main risk factor for the presence of MRSA as a causal agent of bacteremia in the ICU of the hospital network in the city of Bogotá, Colombia. The previous use of vascular and urinary catheters had a similar effect. The presence of these histories should serve as an alert to identify at-risk populations so as to anticipate and prevent the negative consequences of MRSA infection (7). Our study suggests that for *S. aureus* infections, the combined exposure to antibiotics and poor measures to control the infections increase the risk of resistance, as demonstrated with other microorganisms (22).

In Latin America, a study by Porto, *et al.* demonstrated a similar relationship between the presence of MRSA and the use of high dosages of cephalosporins, carbapenems and vancomycin as a monotherapy or in combination (10). As shown in figure 1, we independently identified the effects of the different types of antibiotics on the emergence of MRSA. The present study shows that the previous use of carbapenems has a significant effect on the emergence of methicillin resistance, followed by other effects also reported in the literature such as previous use of vancomycin, quinolone and beta-lactams (in order of importance) (23). This result can be found online in an earlier investigation by Tacconelli, *et al.,* which identified the association of this family of antibiotics with the emergence of resistant microorganisms in hospitals, indicating patterns of consuming broad spectrum antimicrobials which should be reviewed locally (24). The indiscriminate use of antibiotics has been described as a factor that exerts selection pressure on *S. aureus* resistant clones in the health-care setting (8).

The use of invasive devices as a risk factor for the presence of MRSA in bloodstream infections has been proven by earlier studies, as reported by Carnicer-Pont, *et al.* (12). The study by Porto, *et al.* also determined that a history of vascular, respiratory and gastric catheters represented a risk factor (10). The increased risk of MRSA infection can be explained by factors such as bacterial colonization of devices, greater exposure to manipulation and therefore to cross-transmission, and increased exposure to the use of prophylactic antimicrobials which could have a selective effect on the microorganism. An investigation performed at the same time as this study in one of the participating institutions identified a clonal spread of *S. aureus* among patients in the ICU, demonstrating this microorganism's enormous potential for cross-transmission (25).

The presence of comorbidities and the immunological status of patients have been presented previously as risk factors for the presence and prognosis of MRSA as a causal agent of bacteremia (9,10). Nevertheless, this was not proven in the study population. These variables may have been underreported due to the quality of the information given the retrospective nature of the information and the difficulty of verification with patient interviews.

Table 1. Bivariate analysis using conditional logistic regression for factors associated with the emergence of methicillin-resistant *S. aureus* bacteremia

Variables	MRSA (N=186)	MSSA (N=186)				
Risk factors	**n**	**n**	**p**	**OR**	**CI 95%**	
Sex (female)	70	81	0.250	1.27	0.843	1.921
Age (average SD)	58 (19.26)	58 (19.66)	0.918	0.99	0.988	1.010
Immunosuppression *	94	85	0.340	1.22	0.807	1.845
Uncontrolled diabetes	38	28	0.169	1.46	0.849	2.533
Organ failure	30	28	0.775	1.09	0.619	1.900
Cancer	18	15	0.579	1.23	0.593	2.547
Burns	11	11	1.000	1.00	0.343	2.914
Others	26	23	0.512	1.24	0.650	2.367
Comorbidities*						
Congestive heart failure	36	47	0.082	0.64	0.387	1.058
Chronic pulmonary disease	31	37	0.319	0.76	0.450	1.295
Acute myocardial infarction	25	34	0.137	0.64	0.359	1.150
Renal disease (>moderate)	31	28	0.741	1.09	0.628	1.922
Cerebrovascular disease	20	26	0.255	0.69	0.372	1.299
Diabetes mellitus type 2	40	32	0.292	1.32	0.786	2.225
Peripheral vascular disease	17	11	0.291	1.52	0.695	3.348
Cancer	20	17	0.601	1.20	0.604	2.386
Others	48	42	0.690	1.11	0.659	1.875
Previous hospitalization	105	88	0.316	1.33	0.762	2.316
Previous ICU stay	33	23	0.219	1.46	0.795	2.712
Previous surgery	125	73	0.000	3.37	2.180	5.225
Invasive devices when admitted to hospital	86	78	0.363	1.23	0.787	1.924
Type of devices*						
Central vascular accesses	166	128	0.000	4.78	2.574	8.900
Respiratory devices	136	88	0.000	3.32	2.103	5.248
Urinary catheters	145	66	0.000	3.04	1.868	4.960
Gastrointestinal devices	92	64	0.002	2.03	1.298	3.179
Others	18	6	0.016	3.18	1.239	8.198
Devices prior to bacteremia during hospitalization	176	158	0.002	3.59	1.629	7.926
Type of devices*						
Central vascular accesses	64	37	0.001	2.21	1.361	3.603
Respiratory devices	47	18	0.000	3.22	1.780	5.845
Urinary catheters	29	9	0.001	3.62	1.666	7.907
Gastrointestinal devices	34	11	0.000	3.59	1.756	7.357
Others	18	6	0.782	0.86	0.289	2.544
Antibiotic use prior to bacteremia*	143	57	0.000	7.88	4.893	12.716
Prior to hospitalization	52	22	0.000	3.92	2.005	7.668
During hospitalization	130	44	0.000	8.41	5.151	13.755
Type of antibiotic prior to bacteremia*						
Beta-lactams	129	42	0.000	8.48	5.209	13.826
Carbapenems	46	4	0.000	15.46	5.420	44.143
Aminoglycosides	34	5	0.000	8.31	3.158	21.888
Quinolone	26	3	0.000	10.21	3.021	34.544
Vancomycin	30	9	0.000	4.23	1.890	9.474
Place where bacteremia was acquired			0.003	1.34	1.104	1.629
Community**	13	36				
Referring institution	26	26	0.015	1.26	1.229	6.840
Hospital, not ICU	42	35	0.002	3.36	1.544	7.340
Hospital, in the ICU	105	89	0.001	3.35	1.659	6.767
Source of infection is known	127	132	0.563	0.87	0.555	1.377
Primary infection site						
Vascular	73	74	0.913	0.97	0.635	1.499
Respiratory	24	32	0.238	0.75	0.426	1.318
Skin and soft tissues	18	17	0.859	1.07	0.530	2.137
Others	12	9	NS			

*: Not mutually exclusive variables, **: Reference category, NS: not significant

Table 2. Factors associated with the emergence of methicillin-resistant *S. aureus* bacteremia: Multivariate analysis using conditional logistic regression

Associated factor	OR	p	CI	
Previous surgery	1.760	0.037	1.034	2.994
Number of previous intravenous antibiotics*				
One	4.565	0.000	2.541	8.203
Two	12.405	0.000	5.286	29.111
Three or more	31.742	0.000	8.967	112.367
Urinary catheters prior to hospitalization	2.559	0.019	1.170	5.596
Central vascular catheters prior to hospitalization	1.986	0.038	1.038	3.801

Pseudo R^2=0.3115. * Reference category: no previous exposure

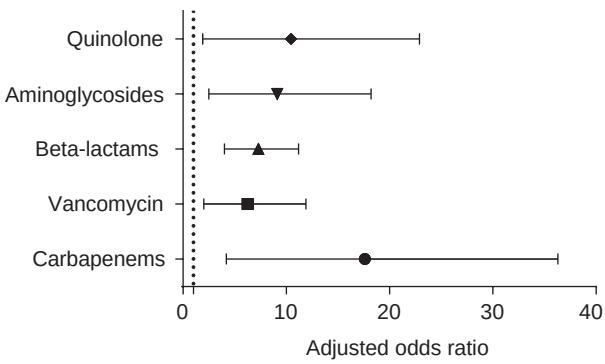

Figure 1. Adjusted effect of the type of antibiotic on the emergence of methicillin-resistant *S. aureus* bacteremia in the ICU
Estimators adjusted by previous surgery and exposure to vascular, respiratory and urinary catheters

A history of previous surgery was clearly identified as a factor associated with MRSA in the global as well as adjusted models for each type of antibiotic. The main explanation for this may be related to the risk of cross-transmission and intensive exposure to antibiotic use for therapeutic or prophylactic purposes.

Most of the infections were considered to have been hospital-acquired at the treating institution (79.0% MRSA vs. 66.7% MSSA) or the referring institution (14.0% for both groups). We observed a predominance of infections classified as community-acquired among patients with methicillin-sensitive *S. aureus* (13 MRSA vs. 36 MSSA). Although the origin of the bacteremia has been associated with the methicillin resistance level where community-acquired isolations are predominantly sensitive to methicillin (14), the multivariate analysis did not find this to be a risk factor for the presence of MRSA, despite its bivariate association with hospital-acquired infection. We did not perform the molecular definition of the type of isolations and their relationships with community-acquired infection in the present investigation. Some reports in Colombia have described the presence of USA 300 clones related with SCC mec type IV genes in patients with multisensitive MRSA infection (8,23), which changed the predominant clone towards the end of the 2000-2010 decade (22,26).

The present study was retrospective and did not include an active search for bacteremia or colonization. Additional limitations were the lack of assessment of other variables related to the presence of MRSA and the use of devices such as prior colonization of these and other environmental variables. The results obtained from a hospital network contribute to the definition of groups at risk for MRSA infection. The risks were identified as previous exposure to invasive vascular and urinary catheters, a history of previous surgery and previous and intensive exposure to various antibiotics. The recognition of these risk factors serves as a guide for health professionals and services to provide differentiated and anticipatory care consisting of the best selection of the empirical antimicrobial therapy, early identification of failure of the established treatment and the correct implementation of measures to control infections in these patients. In order to mitigate the impact of infection by this microorganism on patients treated in intensive care units, health services need to locally define and implement strategies that enable both the early identification of MRSA infection and evidence-based management of this population.

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Conflict of interests

The authors declare no conflicts of interest.

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