

Pathogenic Significance of Methicillin Resistance for Patients with *Staphylococcus aureus* Bacteremia

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To assess whether methicillin resistance is a microbial characteristic associated with deleterious clinical outcome, we performed a cohort study on 908 consecutive episodes of *Staphylococcus aureus* bacteremia and a case-control study involving 163 pairs of patients matched for preexisting comorbidities, prognosis of the underlying disease, length of hospitalization, and age. Of 908 bacteremic episodes, 225 (24.8%) were due to methicillin-resistant *S. aureus* (MRSA). Multivariate analysis did not reveal that methicillin resistance was an independent predictor for mortality when shock, source of bacteremia, presence of an ultimately or rapidly fatal underlying disease, acquisition of the infection in an intensive care unit (ICU), inappropriate empirical therapy, female sex, and age were taken into account. Nonetheless, methicillin resistance was an independent predictor for shock. The case-control study could not confirm that shock was linked to MRSA when prior antimicrobial therapy, inappropriate treatment, ICU residence, and female sex were considered. Our data suggest that cohort studies tend to magnify the relationship of MRSA with clinical markers of microbial pathogenicity and that this effect is a shortcoming of these kind of studies that is caused by inadequate control for underlying diseases.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first described in 1961 [1], and since then, it has become a worldwide problem. Continuous efforts to control MRSA transmission in hospitals may be justified on epidemiological, financial, and clinical bases [2]. When, in a given setting, MRSA accounts for >5%–10% of clinical *S. aureus* isolates, the use of glycopeptides may increase substantially [3]. Vancomycin and teicoplanin are not only notoriously expensive but also ecologically dangerous in an era of emerging resistant gram-positive pathogens like vancomycin-resistant *Enterococcus* [4] and *S. aureus* intermediately resistant to glycopeptides [5]. On the other hand, the spreading behavior of MRSA in hospitals is widely recognized, and serious infections caused by this pathogen, like bacteremia, may significantly affect the overall rate of nosocomial infections [6].

On clinical grounds, control of MRSA would be a requirement of good medical practice if there were evidence that this pathogen had a singular virulence. In fact, on the basis of several studies showing that MRSA does not influence outcome when major confounders such as age, length of hospital stay, comorbidity, general clinical condition, and appropriate treatment [7–15] are taken into account, some investigators have

questioned whether the expense of vigorous infection control policies are worthwhile [15]. However, during the last few years, other studies have suggested that methicillin resistance is independently associated with mortality due to *S. aureus* infections, particularly bacteremia and pneumonia [16–20]. Controversy surrounding MRSA virulence compared with that of methicillin-susceptible *S. aureus* (MSSA) may linger in part because of methodological shortcomings of published investigations. In the present study, a large series of patients with *S. aureus* bacteremia were analyzed to present additional data about the impact of methicillin resistance on selected aspects of the infectious process and outcome.

Patients and Methods

Setting. The Hospital Clínic in Barcelona, Spain, is a 900-bed university center that provides specialized medical and surgical care and is equipped with an intensive care unit (ICU) and a postsurgical unit. Kidney, liver, heart, and bone marrow transplantations are performed, but the hospital lacks a burn unit.

Microbiological methods. During the 8-year study, blood cultures were processed by an automatic nonradiometric system. Isolates were identified according to standard techniques. Methicillin susceptibility was assessed by determining the MIC (microdilution) according to methodology of the National Committee for Clinical Laboratory Standards [21].

Patient description. The present study focuses on episodes of significant monomicrobial bacteremia due to *S. aureus* that were diagnosed from January 1991 to December 1998 at a single center. Patients were consecutively enrolled in the study and prospectively followed up. During the study period, there were 944 episodes of

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significant *S. aureus* bacteremia, of which 908 were monomicrobial. The following data were obtained for all patients: age, sex, pre-existing comorbidities, prognosis of the underlying disease, prior antibiotic therapy, prior surgery, current administration of >20 mg of corticosteroids/d, current administration of antineoplastic chemotherapy, source of bacteremia, leukocyte count, ICU admission, origin of the infection (community- or hospital-acquired), length of hospitalization before diagnosis of bacteremia, need for mechanical ventilation, empirical and definitive antibiotic treatment, susceptibility to methicillin of the involved strain, presence of shock, and related mortality.

Study design. Two types of studies were performed involving patients with *S. aureus* bacteremia. The first was a population-based cohort study that used nonconditional logistic regression methods with shock and death as dependent variables. The second was a case-control study that used conditional logistic regression to check for possible shortcomings of the previous cohort study about the influence of MRSA on shock and outcome.

Definitions of terms. Staphylococcal bacteremia was defined as at least 1 blood culture positive for *S. aureus* and clinically apparent signs and symptoms of sepsis. Comorbidity was defined as a disease or therapy that could predispose patients to infection, alter defense mechanisms, or cause functional impairment, such as the following: diabetes; liver cirrhosis; renal failure; alcoholism (>100 g of alcohol/d); active neoplastic disease; solid organ or bone marrow transplantation; neutropenia; severe chronic obstructive pulmonary disease; severe cardiac disease with symptomatic heart failure; severe dementia; and administration of immunosuppressive drugs (≥ 20 mg of corticosteroids/d on a regular basis or antineoplastic chemotherapy). HIV infection was considered separately. Prognosis of the underlying disease was classified, according to

modification of the criteria of McCabe and Jackson [22], as rapidly fatal (when death was expected within <3 months), ultimately fatal (when death was expected within a period of >3 months but <5 years), and nonfatal (when life expectancy was ≥ 5 years).

Prior antibiotic therapy was defined as use of any antimicrobial agent for ≥ 7 days during the month prior to the occurrence of the bacteremic episode. Prior surgery was defined as any procedure requiring at least 3 days of hospitalization within the last month. Bloodstream infections were considered nosocomial when cultures of blood specimens obtained >48 h after admission were positive [23]; otherwise, the bacteremic episode was considered community-acquired. Antibiotic treatment, either empirical or definitive, was considered appropriate if at least 1 of the antibiotics had in vitro activity against the strain involved and the dose and route of administration were adequate. Shock was defined as a systolic pressure of <90 mm Hg that was unresponsive to fluid treatment or required vasoactive drug therapy [24]. Death was considered related to the bloodstream infection if it occurred before the resolution of symptoms or signs or within 7 days from the onset of *S. aureus* bacteremia and if there was no other explanation.

Follow-up. Patients were observed from the diagnosis of bacteremia until in-hospital death or discharge.

Statistical analysis. Categorical variables were compared by the χ^2 test with Yates' correction or Fisher's exact test when necessary, and continuous variables were compared by the Student's *t* or Mann-Whitney *U* test. Variables with a $P \leq .2$ in the univariate analysis were further analyzed by use of a stepwise nonconditional (population-based cohort study) or conditional (case-control study) logistic procedure with a limit for entering terms of 0.1. Age and length of hospitalization were introduced as continuous variables in decades and multiples of 10, respectively. For the purpose of

Table 1. Comparison of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia in the cohort study.

Clinical characteristic ^a	MRSA bacteremia (n = 225)	MSSA bacteremia (n = 683)	P
Mean age (y) \pm SD	62.5 \pm 17	57.3 \pm 21	.0007
Female	87 (39)	223 (33)	.09
HIV infection	12 (5)	67 (10)	.038
Other preexisting comorbidities	197 (88)	564 (83)	.07
Prognosis of underlying disease ^a			
Nonfatal	95 (42)	358 (52)	
Ultimately fatal	112 (50)	302 (44)	
Rapidly fatal	18 (8)	23 (3)	.0017
Septic metastases	8 (4)	57 (8)	.015
Source of bacteremia			
Low-risk	117 (52)	364 (53)	
Intermediate-risk	67 (30)	186 (27)	
High-risk	41 (18)	133 (19)	.7
Prior antibiotic therapy	138 (61)	158 (23)	<.00001
Bacteremia acquired in hospital	181 (80)	352 (52)	<.00001
Mean length of hospital stay, d	18	8	<.00001
Bacteremia acquired in ICU	59 (26)	91 (13)	<.00001
Mechanical ventilation	18 (8)	17 (2)	.0002
Prior surgery	60 (27)	106 (16)	.0002
Inappropriate empirical therapy	107 (48)	82 (12)	<.00001
Shock	41 (18)	47 (7)	<.00001
Related mortality	49 (22)	61 (9)	<.00001

NOTE. Data are no. (%) of patients unless stated otherwise. ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

^a Classified according to modification of the criteria of McCabe and Jackson [22].

Table 2. Association between clinical variables and risk of shock and mortality in the cohort study of patients with *Staphylococcus aureus* bacteremia.

Clinical characteristic	Shock			Mortality		
	Yes (n = 88)	No (n = 820)	P	Yes (n = 110)	No (n = 798)	P
Mean age (y) \pm SD	64.3 \pm 15	57.9 \pm 20	.0004	64.7 \pm 16	57.7 \pm 20	.0007
Female	31 (35)	279 (34)	.8	44 (40)	266 (33)	.16
HIV infection	3 (3)	76 (9)	.063	7 (6)	72 (9)	.35
Other preexisting comorbidities	79 (90)	682 (83)	.11	99 (90)	662 (83)	.06
Prognosis of underlying disease ^a						
Nonfatal	38 (43)	415 (51)		37 (34)	416 (52)	
Ultimately fatal	39 (44)	375 (46)		52 (47)	362 (45)	
Rapidly fatal	11 (13)	30 (4)	.0007	21 (19)	20 (3)	<.00001
Septic metastases	8 (9)	57 (7)	.45	7 (6)	58 (7)	.7
Source of bacteremia						
Low-risk	28 (32)	453 (55)		26 (24)	455 (57)	
Intermediate-risk	29 (33)	224 (27)		32 (29)	221 (28)	
High-risk	31 (35)	143 (17)	<.00001	52 (47)	122 (15)	<.00001
Prior antibiotic therapy	48 (55)	248 (30)	<.00001	51 (46)	245 (31)	.001
Bacteremia acquired in hospital	55 (63)	478 (58)	.44	64 (58)	469 (59)	.9
Median length of hospital stay, d	14.5	9	.25	15	9	.056
Bacteremia acquired in ICU	21 (24)	129 (16)	<.051	28 (25)	122 (15)	.007
Mechanical ventilation	14 (16)	21 (3)	<.00001	16 (15)	19 (2)	<.00001
Prior surgery	17 (19)	149 (18)	.7	21 (19)	145 (18)	.8
Inappropriate empirical therapy	21 (24)	168 (20)	.45	33 (30)	156 (20)	.01
Shock				49 (45)	39 (5)	<.00001
Related mortality	49 (56)	61 (7)	<.00001			
Methicillin-resistant <i>S. aureus</i>	41 (47)	184 (22)	<.00001	49 (45)	176 (22)	<.00001

NOTE. Data are no. (%) of patients unless stated otherwise. ICU, intensive care unit.

^a Classified according to modification of the criteria of McCabe and Jackson [22].

analysis, the source of bacteremia was divided into 3 categories: low-risk (related mortality rate, <10%), which were iv catheter, urinary tract, ear-nose-larynx, gynecologic, and several manipulation-related sources (including digestive endoscopy, arterial catheterization, and sclerosis of esophageal varices); intermediate-risk (associated mortality rate, 10%–20%), which were osteoarticular, soft-tissue, and unknown sources; and high-risk sources (mortality rate, >20%), which were endovascular, lower respiratory tract, abdominal sources, and CNS foci.

In the case-control study, each patient with MRSA bacteremia (case patient) was matched with a patient with MSSA bacteremia (control patient) who was selected according to the same main underlying disease, prognosis of the underlying disease, and length of hospitalization from admission to diagnosis of the bloodstream infection (stratified as described elsewhere [7] in 4 categories: <72 h, 3–7 days, 8–28 days, and >28 days). When several control patients matched for all these variables, the 1 with the nearest age to the case patient and, if possible, the same sex was selected. If several control patients had all the characteristics, 1 was selected at random. Control patients were chosen without the knowledge of the patients' conditions with regard to shock and survival. The final logistic models contained those variables selected by the stepwise procedure that improved the log likelihood (log likelihood ratio test; $P < .05$) of the model previously built according to the P value for entry at each step [25]. In the case-control study, conditional logistic regression was also used to calculate the OR and 95% CI for related mortality and shock after adjusting for the variables selected by the stepwise procedure. All calculations were performed by means of the 2D, 3D, 4F, and LR programs (BMDP/DYNAMIC Release 7.0; BMDP Statistical Software, Los Angeles).

Results

During the study period, there were 908 episodes of significant monomicrobial bacteremia due to *S. aureus*, of which 225 (24.8%) were caused by MRSA. The mean age \pm SD of the entire group of patients was 58.6 ± 20 years (median, 62 years), and most (598 [66%]) of the patients were male. Eighty-eight patients (9.7%) developed shock, and 110 (12.1%) died in relation to the septic episode. Sources of bacteremia, in descending order of frequency, were as follows: iv catheter (447 patients [49.2%]); unknown (131 [14.4%]); soft tissues, including surgical wounds (103 [11.3%]); endovascular sites other than iv catheters (84 [9.3%]); lower respiratory tract (64 [7%]); urinary tract (25 [2.8%]); intra-abdominal organs (20 [2.2%]); bone and joints (19 [2.1%]); and other (15 [1.7%]).

The differential characteristics of patients with MRSA bacteremia and those with MSSA bacteremia are shown in table 1. MRSA strains originated more frequently from the lower respiratory tract than did MSSA strains (10.2% vs. 6%, respectively; $P = .03$), and MSSA strains originated more frequently from endocarditis than did MRSA strains (11.2% vs. 3.1%, respectively; $P = .0002$). However, when sources of bacteremia were grouped by risk category, MRSA and MSSA strains were equally distributed among low-, intermediate-, and high-risk sources ($P = .7$). In addition, patients with MRSA bacteremia were more likely than those with MSSA bacteremia to be older, to have a rapidly or ultimately fatal underlying disease, to receive prior antimicrobial therapy, to acquire the

Table 3. Clinical features selected by nonconditional logistic regression analysis that were independently associated with shock and related mortality in the cohort study of patients with *Staphylococcus aureus* bacteremia.

Dependent variable, high-risk factor	OR (95% CI)
Shock	
Age	1.13 (1.02–1.26) ^a
Prognosis of underlying disease ^b	
Nonfatal	Comparison group
Ultimately fatal	1.02 (0.62–1.69)
Rapidly fatal	3.38 (1.5–7.63)
Source of bacteremia	
Low-risk	Comparison group
Intermediate-risk	1.94 (1.11–3.41)
High-risk	3.22 (1.78–5.84)
Prior antibiotic therapy	2.03 (1.21–3.4)
Mechanical ventilation	3.31 (1.49–7.31)
Methicillin-resistant <i>S. aureus</i>	1.94 (1.16–3.24)
Related mortality	
Age	1.17 (1.05–1.31)
Female	1.71 (1.02–2.84)
Prognosis of underlying disease ^b	
Nonfatal	Comparison group
Ultimately fatal	2.02 (1.18–3.44)
Rapidly fatal	13.1 (5.7–30.9)
Source of bacteremia	
Low-risk	Comparison group
Intermediate-risk	2.29 (1.21–4.31)
High-risk	9.49 (5.1–17.6)
Shock	12.6 (7.2–22.2)
Inappropriate empirical therapy	2.13 (1.21–3.75)
Bacteremia acquired in ICU	2.09 (1.15–3.78)

NOTE. ICU, intensive care unit.

^a Estimated risk increase for every 10 years of age.

^b Classified according to modification of the criteria of McCabe and Jackson [22].

infection in the hospital, to stay longer in the hospital before the development of bacteremia, to acquire the infection in an ICU, to require mechanical ventilation, to have surgical procedures, to receive inappropriate empirical treatment, to develop shock, and to die as a consequence of the infection. In the group of patients with MRSA bacteremia, there was a non-significant trend for a higher proportion of women ($P = .09$) and for a higher number of patients with an underlying disease different than HIV infection ($P = .07$). Conversely, patients with MSSA bacteremia more frequently had septic metastases ($P = .015$) and HIV infection ($P = .038$) than did those with MRSA bacteremia.

Results of univariate and multivariate analyses of the association of possible risk factors with shock and death in the population-based cohort study are shown in tables 2 and 3, respectively. Methicillin resistance was not an independent predictor for mortality when shock, source of bacteremia, prognosis of the underlying disease, sex, age, acquisition of the infection in an ICU, and appropriateness of empirical treatment were considered. However, methicillin resistance was an independent predictor for shock, as were mechanical ventilation, source of the bacteremia, rapidly fatal prognosis of the underlying diseases, prior antibiotic administration, and age.

There were 163 pairs of case and control patients who were matched completely for underlying disease, prognosis for the underlying disease, and hospitalization length. Diseases defining pair matching were as follows: no disease, 19 pairs; heart disease, 16; chronic obstructive pulmonary disease, 7; diabetes mellitus, 18; liver cirrhosis, 18; renal failure, 22; hematologic neoplasia, 19; solid neoplasia, 20; HIV infection, 8; organ transplantation, 5; and other diseases, 11. Prognosis of the underlying disease was nonfatal for 72 pairs, ultimately fatal for 86, and rapidly fatal for 5. Univariate analysis showed that case patients were still more likely than control patients to receive prior antimicrobial therapy, to receive inappropriate empirical treatment, to develop shock, to require mechanical ventilation, to have a low-risk source of bacteremia, and to die as a consequence of the infection (table 4). A nonsignificant trend was also noted among case patients toward overrepresentation of women, ICU residence, and longer hospitalization before diagnosis of bacteremia. However, stepwise conditional logistic regression analysis selected only prior antimicrobial therapy (OR, 6.71; 95% CI, 3.2–14.1), inappropriate therapy (OR, 9.52; 95% CI, 4.29–21.27), ICU admission (OR, 2.34; 95% CI, 1.03–5.29), and female sex (OR, 3.38; 95% CI, 1.31–8.69) as variables independently associated with MRSA bacteremia. When these characteristics were taken into account, the apparent association of shock and mortality with MRSA were no longer significant (shock: OR, 2.19; 95% CI, 0.85–5.6; death: OR, 1.74; 95% CI, 0.79–3.78).

Discussion

It is well known that patients with bloodstream infections due to MRSA are more likely than patients with MSSA bacteremia to have serious underlying diseases, poor clinical prognosis, longer hospitalization, and prior antibiotic therapy [7–20]. All these characteristics together with an increasing frequency of surgical procedures, ICU residence, need for mechanical ventilation, shock, and mortality have been observed also for patients with MRSA bacteremia in the present cohort study. With this patient profile, it may be difficult to attribute a particular virulence to MRSA, defined in terms of morbidity or mortality, since preexisting underlying diseases, source of infection, shock, and appropriateness of antibiotic therapy have an important impact on survival [26–29]. In fact, the nonconditional logistic regression analysis used in the cohort study did not include methicillin resistance as an independent predictor for mortality when shock, source of bacteremia, prognosis of the underlying disease, sex, age, appropriateness of empirical treatment, and acquisition of bacteremia in an ICU were considered. In the present series, shock and a high-risk source of bacteremia (endovascular, lower respiratory tract, abdominal, or CNS focus) were the variables most strongly associated with death. These findings differ from those of other recent investigations involving patients with staphylococcal bacteremia that

Table 4. Comparison of patients with bacteremia due to methicillin-resistant *Staphylococcus aureus* (case patients) and those with bacteremia due to methicillin-susceptible *S. aureus* (control patients).

Clinical characteristic	Case patients (n = 163)	Control patients (n = 163)	P
Mean age (y) \pm SD	63.4 \pm 14	63.8 \pm 16	.8
Female	65 (39.9)	51 (31.3)	.09
Septic metastases	6 (3.7)	9 (5.5)	.42
Source of bacteremia			
Low-risk	109 (66.9)	85 (52.1)	
Intermediate-risk	36 (22.1)	51 (31.3)	
High-risk	18 (11)	27 (16.6)	.02
Prior antibiotic therapy	94 (57.7)	43 (26.4)	<.00001
Bacteremia acquired in hospital	123 (75.5)	130 (79.8)	.35
Median length of hospital stay, d	15	11	.1
Bacteremia acquired in ICU	40 (24.5)	28 (17.2)	.1
Mechanical ventilation	13 (8)	4 (2.5)	.02
Prior surgery	40 (24.5)	37 (22.7)	.7
Inappropriate empirical therapy	74 (45.4)	20 (12.3)	<.00001
Shock	29 (17.8)	12 (7.4)	.0045
Related mortality	33 (20.2)	18 (11)	.022

NOTE. Data are no. (%) of patients unless stated otherwise. ICU, intensive care unit.

used similar multivariate analyses, in which a positive association of MRSA with mortality was found [16, 18]. However, in 1 of these studies [16], shock was not evaluated as an explanatory variable, and in the other [18], the inclusion of resistance to methicillin in the final logistic model could be tentatively traced to the fact that shock and inadequate empirical therapy were related to a lesser extent to MRSA.

Other studies, most of which were case-control investigations, have indicated that methicillin resistance does not seem to influence outcome when important confounders are taken into account [7–15]. However, even though in the present cohort study methicillin resistance was not included in the final model predicting mortality, its apparently clear association with shock could still denote a singular virulence of MRSA. Our data indicate that once shock occurred, the risk of a fatal outcome was high regardless of the infecting strain, but the adjusted OR for shock in patients with MRSA bacteremia was almost 2-fold greater than that for shock in patients with MSSA bacteremia. These findings agree with those of a previous study focusing on ventilator-associated pneumonia due to *Staphylococcus*, in which the presence of bacteremia and shock was more frequent in patients infected with MRSA [20].

Cohort studies showing an independent association of methicillin resistance with mortality have been criticized as being prone to overestimation of MRSA virulence because of poor adjustment for underlying diseases or severity of clinical condition [7]. A similar criticism could be raised about the association of MRSA with shock, since it is, like mortality, a complex process highly influenced by variables related to prior clinical condition and hemodynamic status [27]. The need for controlling these important confounders is further highlighted by the failure of several basic studies to find differences among MRSA and MSSA strains with regard to possible virulence

markers (such as adherence capacity [30, 31]; intraleukocytic survival [32, 33]; and production of hemolysins, enzymes, and toxins [34–37]); or outcome of experimentally induced infections [34, 35, 37]. Only 1 study reported that lipase production by MRSA was more frequent than that by control strains [38].

We included preexisting comorbidities and prognosis of the underlying disease as putative explanatory variables for shock and related mortality in our cohort study. However, pooling together several comorbidities may not be the best way to account for the different risks of infectious complications, including shock. The same can be said about prognosis of the underlying disease that was based on modification of the criteria of McCabe and Jackson [22], whose classification “ultimately fatal” may be too broad to be meaningful enough in this context. To check for these eventual shortcomings in our cohort series, we performed a case-control study that took advantage of the large number of patients we had the opportunity to investigate.

One hundred sixty-three patients with MRSA bacteremia (case patients) could be matched on an individual basis with patients with MSSA bacteremia (control patients) who had the same kind of preexisting comorbidities, prognosis of the underlying disease, and length of hospitalization before diagnosis of the septic episode. After matching, case patients were still more likely than control patients to have prior antimicrobial therapy, to receive inappropriate empirical treatment, to develop shock, to require mechanical ventilation, to be female, to acquire the infection in an ICU, to stay longer in the hospital, and to die as a consequence of the infection. However, when shock and death were included in a conditional logistic regression model after controlling for variables selected by the stepwise procedure as independently associated with case patients (prior antimicrobial therapy, inappropriate empirical therapy, sex, and acquisition of bacteremia in an ICU), mortality and shock were no longer significantly linked to MRSA. We believe that the only real particularity of our case-control study was the strict adjustment for underlying diseases, since prognosis of the underlying disease and length of hospitalization had a good possibility of being influential in the multivariate analysis of the cohort study.

In summary, the present data suggest that cohort studies tend to magnify the relationship of MRSA with clinical markers of microbial pathogenicity and that this effect stems from inadequate control for underlying diseases. If MRSA has any particular tendency to induce shock compared with MSSA, it appears that this tendency is, at most, marginal.

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