Outcome and Attributable Mortality in Critically Ill Patients With Bacteremia Involving Methicillin-Susceptible and Methicillin-Resistant Staphylococcus aureus

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Background: Staphylococcus aureus bacteremia carries high mortality rates. The clinical impact of methicillin resistance remains controversial: outcome comparisons between patients with bacteremia involving methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) S. aureus are difficult to perform because of important differences in severity of illness.

Methods: A retrospective cohort analysis and 2 independent case-control analyses were performed to determine and compare outcomes and attributable mortality rates of MSSA (n=38) and MRSA bacteremia (n=47) in critically ill patients. For the case-control studies, matching (1:2 ratio) was based on the APACHE (Acute Physiology and Chronic Health Evaluation) II classification: APACHE II score (±1 point) and diagnostic category.

Results: Patients with MRSA bacteremia had more acute renal failure and hemodynamic instability than patients with MSSA bacteremia. They had a longer intensive care unit stay and ventilator dependency.

Patients with MRSA bacteremia had a higher 30-day mortality rate (53.2% vs 18.4%) and in-hospital mortality rate (63.8% vs 23.7%) (P<.05). Multivariate survival analysis demonstrated acute renal failure, length of mechanical ventilation, age, and methicillin resistance to be independently associated with mortality (P<.05). The attributable mortality rate for MSSA bacteremia was 1.3%: mortality rates for cases and controls were respectively 23.7% and 22.4% (P=.94). The attributable mortality rate for MRSA bacteremia was 23.4%: mortality rates for cases and controls were respectively 63.8% and 40.4% (P=.02). The difference (22.1%) between both attributable mortality rates was significant (95% confidence interval, 8.8%-35.3%).

Conclusion: In critically ill patients, after accurate adjustment for disease severity and acute illness, we found MRSA bacteremia to have a higher attributable mortality than MSSA bacteremia.

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THE INCIDENCE of Staphylococcus aureus bacteremia in hospitals as well as communities has significantly increased over the past decades.1 Staphylococcus aureus has become the leading cause of both community-acquired and nosocomial bacteremia. Particularly in intensive care units (ICUs) where nosocomial bacteremia is one of the leading cause of death associated with nosocomial infections, S. aureus is a feared pathogen. Because of its ability to cause severe infections and spread by metastatic foci, S. aureus is considered extremely virulent. In general, fatality rates range from 20% to 50%.2-8

With the emergence of methicillin resistance, S. aureus has received even more attention as bacteremia involving methicillin-resistant S. aureus (MRSA) are causing higher hospital costs,2,9 and therapeutic options are limited to the use of glycopeptides. Besides this, it is uncertain if methicillin resistance affects the outcome.

MATERIALS AND METHODS

SETTING

The present study was conducted in the 1060-bed Ghent University Hospital (Ghent, Belgium) and performed in a subset of critically ill patients. The ICU has 54 beds and includes a medical and surgical ICU, a unit for cardiac surgery, and a burn unit. An average of 3300 patients are admitted to the ICU each year. In the global ICU population, no changes in age, length of ICU stay, or APACHE (Acute Physiology and Chronic Health Evaluation) II scores were observed during the study period.

STUDY OBJECTIVE AND DESIGN

The aim of this study was to compare population characteristics, outcomes, and attributable mortality in adult ICU patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus.
teremia involving methicillin-susceptible \textit{S aureus} (MSSA) and MRSA. A retrospective population-based cohort study of patients with MSSA or MRSA bacteremia from January 1992 through December 1998 was performed. All microbiologically documented bloodstream infections were prospectively screened by the local center for infection control. This case-based surveillance system was used for the retrospective search for all ICU patients whose ICU stay was complicated with \textit{S aureus} bacteremia during the study period.

In addition, to adjust for differences in severity of illness, attributable mortality rates for MSSA and MRSA bacteremia were determined and compared. Two independent case-control studies were performed: a MSSA case-control study and a MRSA case-control study. In each case-control study, every case patient (defined as patient with \textit{S aureus} bacteremia) was matched with 2 other ICU patients (1:2 ratio) without clinical or microbiologically evidence of \textit{S aureus} bacteremia (matched controls). Matching was based on the APACHE II classification\(^{10}\): an equal APACHE II score (±1 point) and an equal principal diagnosis leading to ICU admission (diagnostic category). The APACHE II classification is considered a standard for the comparison of severity of illness in ICU patients. The APACHE II score is calculated on the basis of a long-term health evaluation and a set of acute physiologic parameters obtained during the first 24 hours of ICU observation. Because expected in-hospital mortality rate can be calculated with the APACHE II score and a factor attributed to a precise diagnostic category (surgical vs nonsurgical admission diagnosis, elective or urgent surgery, major vital organ system of failure, and the principal diagnosis leading to ICU admission), this matching procedure resulted in an equal expected mortality rate for cases and controls.\(^{10}\) Therefore, this severity of disease scoring system has been repeatedly used for case-control studies dealing with nosocomial infections in ICU settings.\(^{11-13}\) To reduce the risk of selection bias, matching was done on a 1:2 ratio. Selection of control subjects was obtained without knowledge of outcome. In case of there being more than 2 potential controls, matching was based on the nearest admission date of the case. All control patients were selected from the study period in which the cases were detected.

**DEFINITIONS**

\textit{Staphylococcus aureus} bacteremia is defined as the microbiologically documented presence of \textit{S aureus} in the blood. All ICU patients with at least 1 positive hemoculture are included in the study. Hemocultures are taken on a routine basis when infection is clinically suspected or when a patient’s temperature rises above 38.4°C. In this way, only clinically significant bacteremia were included. Hemocultures are executed following the BacT/Alert procedure (Organon Teknika Corp, Durenham, NC), and a 10-ml. blood inoculum is considered standard. Methicillin resistance is determined according to methods recommended by the National Committee for Clinical Laboratory Standards for disk diffusion testing.\(^{14}\)

\textit{Staphylococcus aureus} bacteremia were considered nosocomially acquired when they appeared after 72 hours of hospital admission. The source of the bacteremia was determined by microbiologists and intensivists based on isolation of \textit{S aureus} from the presumed portal of entry and on clinical evaluation.

Antibiotic therapy was considered adequate if the drugs used had in vitro activity against the isolated \textit{S aureus} strain. We considered antibiotic therapy inadequate if the drugs used did not have in vitro activity against the \textit{S aureus} strain or if the patient did not receive antibiotic treatment. Delay in therapy was calculated from the onset of the \textit{S aureus} bacteremia.

Severity of illness was assessed by means of the APACHE II score, a severity of disease classification system.\(^{10}\) Acute renal failure was defined as dialysis dependency, acute respiratory failure as ventilator dependency, and hemodynamic instability as the need for inotropic or vasopressor support during the ICU stay.

The following data were recorded: age, ICU stay, length of hospital stay prior to the onset of the bacteremia, length of ventilator dependency, and the presence of a polymicrobial bacteremia. No study patients were neutropenic (neutrophil count <500/µL).

**OUTCOME**

For the outcome comparison of patients with MSSA and MRSA bacteremia, survival status is checked 15 days and 30 days after the onset of the bacteremia and at the end of the hospital stay, defined respectively as 15-day, 30-day, and in-hospital mortality. When patients with MSSA and MRSA bacteremia are compared with their respective control groups, in-hospital mortality rates are used. Attributable mortality is defined as the excess mortality caused by the bacteremia. It is determined by subtracting the crude mortality rate of the control patients from the crude mortality rate of the cases.\(^{10}\)

**STATISTICAL ANALYSIS**

Continuous variables are described as mean±SD and median (interquartile range). Comparative tests on categorical variables are executed with the Pearsons \(\chi^2\) test and with the Mann-Whitney test on continuous variables.

Survival curves for patients with MSSA and MRSA bacteremia and their respective control groups were prepared according to the Kaplan-Meier method. For the analysis between patients with MSSA and MRSA bacteremia, survival was compared from the onset of the bacteremia. For cases and controls, survival curves are compared from the time of ICU admission. The log-rank test and Wilcoxon test were used to determine significance between survival curves.

To assess relationship between mortality and a set of variables, multivariate survival analyses were executed following the Cox proportional hazards model. In this multivariate analysis, continuous variables are handled as such. Hereby, hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Variables with a \(P\) value greater than .10 were removed from the equation.

For differences between observed mortality and expected mortality rates, as assessed on the basis of the APACHE II classification, 95% CIs are reported. The \(z\) test was used to compare attributable mortality rates of MSSA and MRSA bacteremia. Statistical analyses were performed with \textsc{statistics} 4.5 (Statsoft Inc, Tulsa, Okla) and \textsc{spss} 9.0 (SPSS Inc, Chicago, Ill) software. All tests are 2-tailed, and statistical significance is defined as a \(P\) value less than .03.

**RESULTS**

During the 7-year study period, 22431 patients were admitted to the ICU. In 85 patients a microbiologically documented \textit{S aureus} bacteremia was diagnosed. This represents a prevalence of 3.8 cases of \textit{S aureus} bacteremia in 1000 ICU admissions.

Fifteen patients developed \textit{S aureus} bacteremia within 72 hours of hospital admission. Of these, 12 were MSSA and 3 MRSA bacteremia. In our opinion, these specific \textit{S aureus} bacteremias could not be considered community acquired because none of these patients had septicemia as a principal diagnosis at time of admission
and the *S. aureus* bacteremia was diagnosed after surgery or placement of central venous catheters in all patients.

THE COHORT STUDY (MSSA VS MRSA)

Thirty-eight patients had *S. aureus* bacteremia involving MSSA. An MRSA bacteremia was diagnosed in 47 patients. Population characteristics for both groups are given in Table 1.

There was a significant difference between both groups in ICU stay, time of hospitalization prior to the onset of the *S. aureus* bacteremia, and length of ventilator dependency. Patients with MRSA bacteremia also had more acute renal failure and hemodynamic instability. However, both of these comorbidities were also more present in this group before the onset of the bacteremia. The APACHE II scores and related expected in-hospital mortality rates were significantly higher in the MRSA group.

![Figure 1](https://example.com/f1.png)

**Figure 1.** Survival curves for intensive care patients with bacteremia involving methicillin-susceptible *Staphylococcus aureus* (MSSA) (*n*=58) and methicillin-resistant *S. aureus* (MRSA) (*n*=47) (log-rank test, *P*=.001; Wilcoxon test, *P*<.001).

The MSSA bacteremia case-control study

Population characteristics of cases and controls are shown in Table 2. Compared with their control subjects, patients with MSSA bacteremia had a longer ICU stay, a longer ventilator dependency, and more acute respiratory failure. Despite these differences, the attributable mortality rate for MSSA bacteremia was only 1.3% (95% CI, −15.2% to 17.8%) as in-hospital mortality rates for cases and controls were respectively 23.7% and 22.4% (*P*=.94).

**Figure 2** demonstrates the survival curves for both groups. The mortality rate observed in the control group (22.4%) did not differ from the expected mortality rate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MSSA Bacteremia</th>
<th>MRSA Bacteremia</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59 ± 13.6/60 (49-70)</td>
<td>55 ± 18.9/61 (38-71)</td>
<td>.58</td>
</tr>
<tr>
<td>Hospitalization prior to the bacteremia, d</td>
<td>10 ± 13.0/6 (1-13)</td>
<td>29 ± 26.2/24 (10-36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ICU stay prior to bacteremia, d</td>
<td>8 ± 12.6/4 (1-8)</td>
<td>20 ± 29.0/15 (3-25)</td>
<td>.001</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>18 ± 16.1/14 (3-24)</td>
<td>37 ± 28.7/28 (12-54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presence of polymicrobial bacteremia</td>
<td>6 (16)</td>
<td>10 (21)</td>
<td>.96</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (8)</td>
<td>19 (40)</td>
<td>.002</td>
</tr>
<tr>
<td>Acute renal failure prior to the bacteremia</td>
<td>0</td>
<td>12 (26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute renal failure after onset of the bacteremia</td>
<td>3 (8)</td>
<td>7 (15)</td>
<td>.51</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>32 (84)</td>
<td>43 (92)</td>
<td>.49</td>
</tr>
<tr>
<td>Length of ventilator dependency, d</td>
<td>9 ± 10.6/4 (1-12)</td>
<td>29 ± 26.4/24 (9-41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>17 (45)</td>
<td>35 (75)</td>
<td>.01</td>
</tr>
<tr>
<td>Hemodynamic instability prior to the bacteremia</td>
<td>12 (32)</td>
<td>29 (62)</td>
<td>.01</td>
</tr>
<tr>
<td>Hemodynamic instability after onset of bacteremia</td>
<td>5 (13)</td>
<td>6 (13)</td>
<td>.79</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17 ± 6.9/17 (10-21)</td>
<td>23 ± 8.9/25 (16-28)</td>
<td>.001</td>
</tr>
<tr>
<td>Expected in-hospital mortality rates, %</td>
<td>26 ± 21.2/15 (8-42)</td>
<td>42 ± 28.2/39 (16-65)</td>
<td>.009</td>
</tr>
</tbody>
</table>

Table 1. Population Characteristics for Intensive Care Patients With MSSA and MRSA Bacteremia

*Continuous variables are described as mean ± SD/median (interquartile range); categorical variables are described as number (percentage). MSSA indicates methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S aureus*; ICU, intensive care unit; and APACHE, Acute Physiology and Chronic Health Evaluation.

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A multivariate analysis demonstrated the following variables to be independent predictors of mortality: length of ICU stay (HR, 1.02; 95% CI, 1.01-1.03; P = .001), APACHE II score (HR, 1.04; 95% CI, 1.02-1.06; P = .001), hemodynamic instability (HR, 1.76; 95% CI, 1.14-2.71; P = .01), and MRSA bacteremia (HR, 1.72; 95% CI, 1.10-2.68; P = .02). Acute renal failure reached a level of borderline significance (HR, 1.50; 95% CI, 0.97-2.34; P = .07).

**COMPARISON OF THE ATTRIBUTABLE MORTALITY RATES OF MSSA AND MRSA BACTEREMIA**

The difference between the attributable mortality rates of MSSA bacteremia (1.3%) and MRSA bacteremia (23.4%) was 22.1%. This difference was statistically significant (95% CI, 8.8%-35.3%).

**COMMENT**

Since methicillin resistance has become widespread, the debate whether MRSA bacteremia is associated with higher mortality than MSSA bacteremia has been ongoing. Because of important differences in population characteristics, outcome comparisons are difficult to perform. Patients infected with MRSA tend to be older, sicker, and more debilitated. In contrast with MSSA-infected patients, they mostly have a history of prior antibiotic use and a longer time of hospitalization.5,6,10-22

Previous studies comparing outcomes in MSSA and MRSA bacteremia revealed some conflicting data. Most studies could not find a higher mortality rate among patients with bacteremia involving MRSA.2,17,23-26 Other investigators found significantly higher fatality rates in patients with MRSA bacteremia.27,28 Probably the most powerful study concerning clinical outcomes in patients with MSSA and MRSA bacteremia was performed by Soriano et al.29 These authors compared 225 episodes of MRSA bacteremia with 683 episodes of MSSA bacteremia. In this cohort study, patients with MRSA bacteremia were older and sicker and had, as a consequence, a higher intrinsic mortality rate. Methicillin resistance was associated with shock, a variable recognized to be an independent predictor of mortality. Besides this cohort study, Soriano et al composed 163 matched pairs

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**Table 2. Population Characteristics for Patients With MSSA Bacteremia (Cases) and Their Matched Control Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 38)</th>
<th>Controls (n = 76)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59 ± 13.6/60 (49-70)</td>
<td>57 ± 16.6/60 (48-73)</td>
<td>.70</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>18 ± 16.1/14 (3-24)</td>
<td>11 ± 14.8/5 (2-13)</td>
<td>.02</td>
</tr>
<tr>
<td>Length of ventilator dependency, d</td>
<td>9 ± 10.6/4 (1-12)</td>
<td>5 ± 11.9/0 (9-5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>32 (84)</td>
<td>36 (49)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (6)</td>
<td>8 (11)</td>
<td>.91</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>17 (45)</td>
<td>25 (34)</td>
<td>.30</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17 ± 6.9/17 (10-21)</td>
<td>17 ± 7.1/17 (11-22)</td>
<td>.95</td>
</tr>
<tr>
<td>Expected in-hospital mortality rates, %</td>
<td>26 ± 21.2/15 (8-42)</td>
<td>26 ± 20.6/18 (10-42)</td>
<td>.92</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>9 (24)</td>
<td>17 (22)</td>
<td>.94</td>
</tr>
</tbody>
</table>

*Continuous variables are described as mean ± SD/median (interquartile range); categorical variables are described as number (percentage). MSSA indicates methicillin-susceptible Staphylococcus aureus; ICU, intensive care unit; and APACHE, Acute Physiology and Chronic Health Evaluation.*

(26.0%) as assessed on basis of the APACHE II classification system (95% CI, 13.0%-31.8%).

A multivariate survival analysis showed acute renal failure to be independently associated with fatal outcome (HR, 3.24; 95% CI, 1.6-6.48; P = .001). Hemodynamic instability reached a level of borderline significance (HR, 1.54; 95% CI, 0.99-2.39; P = .06).

**THE MRSA BACTEREMIA CASE-CONTROL STUDY**

Population characteristics of cases and controls are given in **Table 3**. Compared with their controls, patients with MRSA bacteremia had a longer ICU stay, a longer ventilator dependence, more acute renal failure, and more hemodynamic instability. In this case-control analysis, an attributable mortality rate of 23.4% (95% CI, 6.5%-40.3%) was found, since mortality rates for cases and controls were respectively 63.8% and 40.4% (P = .02). Figure 3 demonstrates the survival curves for cases and controls. Although control subjects seem to die earlier, mortality did not significantly differ in the first weeks of ICU stay. Once most case patients developed their MRSA bacteremia (after a mean ICU stay of 20 days), curves cross and diverge further on during ICU and hospital stay. The observed mortality rate in the control group (40.4%) did not differ from the mortality rate that was expected on the basis of the APACHE II classification system (42.4%; 95% CI, 30.5%-50.3%).

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(67x72)
of patients with MSSA and MRSA bacteremia on basis of preexisting comorbidities, prognosis of underlying disease, and length of hospitalization prior to the bacteremia. Notwithstanding this matching procedure, there were still more comorbidity factors and a higher rate of shock and related mortality in the MRSA group. In a logistic regression analysis, methicillin resistance was not independently associated with shock and mortality. Based on this finding, the authors concluded that cohort studies tend to magnify the relationship of MRSA with microbial pathogens by inadequately controlling for underlying disease and, hence, previous studies might have overestimated the pathogenic impact of methicillin resistance. This may also account for our cohort study wherein, notwithstanding adjustments for comorbidity factors and APACHE II score, methicillin resistance appeared to be an independent predictor of mortality.

To overcome major differences in population characteristics and, in particular, severity of illness, we investigated outcomes in MSSA and MRSA bacteremia by means of 2 independent case-control studies, after which attributable mortality rates of MSSA and MRSA bacteremia were compared. Based on a MEDLINE search (April 2001), we assume that this study contains the largest number of exclusive ICU patients. To our knowledge, this study is the first to investigate outcomes between MSSA and MRSA patients by comparing attributable mortality rates obtained by case-control studies.

Crucial for the interpretation of the results is the level of coincidence between cases and controls. The matching procedure used in the case-control studies was based on severity of illness and diagnostic category at the time of ICU admission because these are the most important prognostic indicators in ICU patients with S aureus bacteremia. In both case-control studies, the mortality rates observed in the control groups were nearly equal to the mortality rate that was expected on the basis of the APACHE II classification system. This indicates that we had 2 dependable control groups.

Time-dependent variables such as length of hospitalization prior to the onset of the infection and length of hospitalization may confound outcome studies dealing with nosocomial bloodstream infections. As found in general, and also in our cohort study, length of hospitalization prior to S aureus bacteremia was significantly longer in the MRSA group (Table 1). We question, however, the confounding impact of this variable in our study: length of stay prior to the bacteremia was not associated with fatal outcome in the multivariate survival analysis (cohort study).

Our data revealed that in critically ill patients, MRSA bacteremia carries a higher attributable mortality than bacteremia involving MSSA. The MSSA case-control study revealed a nonsignificant attributable mortality rate of 1.3%, whereas in the MRSA case-control study, an attributable mortality rate of 23.4% was found. In the MRSA case-control study, cases were more likely to have more comorbidities and a longer length of stay in the ICU, as well as a longer length of mechanical ventilation. This seems not to hamper the interpretation of the results. First, in the MSSA case-control study, there was also more acute respiratory failure, a longer ICU stay, and a longer length of ventilator dependency noted in the case patients. In this case-control study, these differences seemed not to affect the outcome. Second, a more rigorous matching procedure taking into account more comorbidities and/or time-dependent variables might have led to overmatching with loss of validity or statistical power.

The fact that MRSA bacteremia carries a significantly higher fatality rate and attributable mortality does not prove causality between methicillin resistance and deleterious outcome. A higher clinical virulence among MRSA strains can be suggested based on studies report-

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**Table 3. Population Characteristics for Intensive Care Patients With MRSA Bacteremia (Cases) and Their Matched Control Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 47)</th>
<th>Controls (n = 94)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55 ± 18.9/61 (38-71)</td>
<td>70 ± 16.4/65 (51-73)</td>
<td>.06</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>37 ± 28.7/28 (12-54)</td>
<td>10 ± 10.9/6 (3-15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of ventilator dependency, d</td>
<td>29 ± 26.4/24 (9-41)</td>
<td>7 ± 9.2/3 (1-9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>43 (92)</td>
<td>72 (18)</td>
<td>.06</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>19 (40)</td>
<td>17 (18)</td>
<td>.008</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>35 (75)</td>
<td>49 (52)</td>
<td>.02</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23 ± 8.9/25 (16-28)</td>
<td>23 ± 8.9/25 (15-28)</td>
<td>.92</td>
</tr>
<tr>
<td>Expected in-hospital mortality rates, %</td>
<td>42 ± 28.2/39 (16-65)</td>
<td>42 ± 28.0/38 (18-66)</td>
<td>.94</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>30 (64)</td>
<td>38 (40)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Continuous variables are described as mean ± SD/median (interquartile range); categorical variables are described as number (percentage). MRSA indicates methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; and APACHE, Acute Physiology and Chronic Health Evaluation.

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**Figure 3.** Survival curves for intensive care patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia (n=47) and their matched control subjects (n=94) (log-rank test, P=.12; Wilcoxon test, P=.40).

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ing a higher infection rate with *S aureus* among nasal carriers of MRSA compared with MSSA-colonized patients.32,34 However, also in this setting, MRSA carriers tend to have a more debilitated physical condition, hampering a fair comparison. Moreover, once nasal *S aureus* colonization has become established, selective antibiotic pressure promotes nasal MRSA colonization to a higher degree than colonization with methicillin-susceptible isolates because MRSA strains are resistant to multiple antimicrobial agents and not exclusively to β-lactams.35 Consequently, MRSA colonization leads to autoinfection at a higher rate than does MSSA colonization.

Several experimental, in vitro studies tried to find stronger virulence attributes in MRSA strains.18,19,36-42 Of all these laboratory investigations, only 1 reported a higher production of lipase in MRSA strains,42 and one found MRSA strains to have a lesser ability to bind to fibronectin compared with MSSA strains.19 These data make us conclude that the virulence of staphylococci is more closely tied to particular strains than to methicillin resistance. This is an interesting finding considering that our analysis was based on single-center experience. Coincidentally, the virulence of an MRSA strain, which is frequently isolated in our ICU, may be very high. This might represent a bias we could not adjust for given the retrospective fashion of our study. Besides the hypothetical differences in clinical virulence between methicillin-susceptible and methicillin-resistant isolates, the restriction in therapeutic options might be a reasonable explanation for the striking difference in attributable mortality between MSSA and MRSA bacteremia. Methicillin-resistant *S aureus* infections are treated with glycopeptides (rifampicin is not licensed for this indication in Belgium), which are less powerful antibiotics than oxacillin or cloxacillin, drugs of choice in the treatment of MSSA infections. In fact, based on a cohort of patients with bacteremic pneumonia involving MSSA, Gonzalez et al34 reported a significantly higher mortality rate in patients treated with glycopeptides compared with patients treated with cloxacillin. Based on this, we assume that the worse outcome in patients with MRSA bacteremia might be a consequence of a less effective antibiotic therapy. With new antibiotic agents against resistant gram-positive infections, such as linezolid, quinupristindalfopristin, and telithromycin, there might be some optimism. However, compared with the currently available glycopeptides (vancomycin and teicoplanin), their clinical benefits in terms of survival remain unclear.

We noted a high rate (26.3%) of inappropriate antibiotic therapy among patients with MSSA bacteremia. Of the 10 patients with inappropriately treated MSSA bacteremia, 3 patients died (2 of whom died before MSSA bacteremia was diagnosed). Although inappropriate treatment was not associated with important excess mortality in our population, it is generally accepted that every *S aureus* bacteremia should be treated promptly. The reason for the high rate of appropriate antibiotic treatment in the MRSA cohort might be our intensive screening policy. In every ICU patient, site-specific surveillance cultures are taken 3 times weekly. In our MRSA cohort, colonization preceded bacteremia in 83% of the patients. Methicillin-susceptible *S aureus* colonization preceded bacteremia in 37% of the cases (data not shown). In this way, intensivists were more often alerted by prior MRSA colonization, resulting in a high rate of appropriate antimicrobial therapy from onset of clinical infection.

### CONCLUSIONS

Following a similar case-control matching procedure, our data revealed that MRSA bacteremia carries a significantly higher attributable mortality than bacteremia involving MSSA. Given the close matching on the basis of APACHE II score and diagnostic category, the higher attributable mortality in MRSA bacteremia cannot be solely due to differences in severity of underlying disease and acute illness. Because there is little evidence of suspecting MRSA strains to be more virulent, the most plausible explanation for the 22.1% higher attributable mortality rate seems to be the less bactericidal potential of glycopeptides compared with oxacillin or cloxacillin. From this we conclude that all efforts to limit the endemic spread of MRSA must go on and, when possible, *S aureus* infections should be treated with oxacillin or cloxacillin.

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