Methicillin-Resistant \textit{Staphylococcus aureus} (MRSA) Staphylococcal Cassette Chromosome \textit{mec} Genotype Effects Outcomes of Patients With Healthcare-Associated MRSA Bacteremia Independently of Vancomycin Minimum Inhibitory Concentration

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\textbf{Background.} Recent evidence has shown that community-associated methicillin-resistant \textit{Staphylococcus aureus} (CA-MRSA) is less virulent than traditional hospital-associated MRSA. We explored whether the antimicrobial susceptibilities of the different strains account for their disparity in clinical virulence.

\textbf{Methods.} This 10-year retrospective cohort study enrolled 291 patients with community-onset, healthcare-associated MRSA bacteremia. The vancomycin minimum inhibitory concentration (MIC) and staphylococcal cassette chromosome \textit{mec} (SCC\textit{mec}) type were determined for all isolates. CA-MRSA was defined as an isolate possessing the SCC\textit{mec} type IV or V genes, and hospital-associated MRSA (HA-MRSA) was defined as an isolate possessing SCC\textit{mec} type I, II, or III genes. Low and high vancomycin MICs were defined as MICs of \( \leq 1 \) and \( \geq 2 \) \( \mu \text{g/mL} \), respectively. Patients with bacteremia due to CA-MRSA with a low vancomycin MIC (\( n = 111 \)), due to HA-MRSA with a low vancomycin MIC (\( n = 127 \)), or due to HA-MRSA with a high vancomycin MIC (\( n = 47 \)) entered the outcome analysis. The outcomes of the 2 HA-MRSA bacteremia groups were compared to those of the CA-MRSA bacteremia group.

\textbf{Results.} Treatment failure was observed in 35 (31.5%), 59 (46.5%), and 27 (57.4%) of patients with low-vancomycin-MIC CA-MRSA, low-vancomycin-MIC HA-MRSA, and high-vancomycin-MIC HA-MRSA bacteremia, respectively. After adjustment for potential confounding factors, the risk of treatment failure was significantly higher among patients with low-vancomycin-MIC HA-MRSA (adjusted odds ratio [aOR], 1.853; 95% confidence interval [CI], 1.006–3.413) and high-vancomycin-MIC HA-MRSA (aOR, 2.393; 95% CI, 1.079–5.309), compared with patients with low-vancomycin-MIC CA-MRSA.

\textbf{Conclusions.} The higher risk for treatment failure among patients with traditional hospital-associated MRSA infections, compared with patients with CA-MRSA infections, is independent of the vancomycin MIC, suggesting a potential intrinsic strain-specific virulence effect.

The emergence of community-associated methicillin-resistant \textit{Staphylococcus aureus} (CA-MRSA) has become a global public health issue \cite{1, 2}. Although the communities in which strains of CA-MRSA are circulating differ geographically, a high prevalence and disease burden of CA-MRSA have been increasingly

\begin{thebibliography}{9}
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\bibitem{2} This 10-year retrospective cohort study enrolled 291 patients with community-onset, healthcare-associated MRSA bacteremia. The vancomycin minimum inhibitory concentration (MIC) and staphylococcal cassette chromosome \textit{mec} (SCC\textit{mec}) type were determined for all isolates. CA-MRSA was defined as an isolate possessing the SCC\textit{mec} type IV or V genes, and hospital-associated MRSA (HA-MRSA) was defined as an isolate possessing SCC\textit{mec} type I, II, or III genes. Low and high vancomycin MICs were defined as MICs of \( \leq 1 \) and \( \geq 2 \) \( \mu \text{g/mL} \), respectively. Patients with bacteremia due to CA-MRSA with a low vancomycin MIC (\( n = 111 \)), due to HA-MRSA with a low vancomycin MIC (\( n = 127 \)), or due to HA-MRSA with a high vancomycin MIC (\( n = 47 \)) entered the outcome analysis. The outcomes of the 2 HA-MRSA bacteremia groups were compared to those of the CA-MRSA bacteremia group.
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observed in many countries [3–5]. Even more alarmingly, reports of severe infections associated with novel CA-MRSA strains, with significant patient morbidity and mortality, are increasing [6–8]. Furthermore, while CA-MRSA strains were initially recognized in community patients without prior history of hospital contact, CA-MRSA strains have now invaded hospital environments to become the predominant nosocomial MRSA isolates [9]. The possibility that CA-MRSA causes a worse patient outcome and a higher nosocomial infection burden than traditional hospital-associated MRSA is therefore a serious concern. However, the few studies specifically addressing the relative disease impacts of CA-MRSA and traditional hospital-associated MRSA report conflicting results [10–16].

Recent studies, however, provide convincing evidence for this important issue and demonstrate that CA-MRSA strains, either MRSA carrying staphylococcal cassette chromosome mec (SCCmec) type IVa [17] or MRSA USA300 clones [18, 19], are associated with less mortality or better clinical outcomes than other MRSA strains. Although these studies elaborated on the relative virulence between different MRSA strains, however, other questions remain to be clarified. Theoretically, an MRSA isolate that originated from the community is expected to be less resistant to various antimicrobial agents than an MRSA isolate that originated from the high-selection-pressure hospital environment. Because the differences in antimicrobial resistance between MRSA strains are highly relevant to clinical outcomes, it is therefore uncertain whether the effect of MRSA strain on treatment outcomes stems from intrinsic virulence factors or simply reflects the inadequacy of antimicrobial therapy due to higher antimicrobial resistance. The vancomycin minimum inhibitory concentrations (MICs) for different MRSA strains are especially important considerations because vancomycin is the most commonly used anti-MRSA agent in many countries. Furthermore, high-vancomycin-MIC MRSA has now been found to be associated with a higher mortality rate among patients with MRSA bacteremia [20].

In this study, we examined the independent effect of MRSA strain on clinical outcomes by classifying bacteremia patients according to the genotype and vancomycin MIC of MRSA isolates recovered from them. We hypothesized first that CA-MRSA has a different clinical impact than traditional hospital-associated MRSA on patient outcomes. We then hypothesized that these differences in outcomes result from the difference in vancomycin MICs between community-associated and hospital-associated MRSA isolates. We limited the study subjects to patients with MRSA bacteremia who had a prior history of healthcare-associated exposure, because patients with true community-acquired infection usually have distinct infection patterns and less comorbidity than patients with healthcare-associated risk, which could severely confound the study results.

**METHODS**

**Study Design, Setting, and Participant Selection**

This retrospective cohort study was conducted in the emergency department (ED) of the National Taiwan University Hospital. This 2500-bed, university-affiliated teaching hospital provides both primary and tertiary care in northern Taiwan and discharges an average of 67,000 patients each year. The initial patient list was retrieved from our ED-based longitudinal epidemiology study of community-onset *S. aureus* bacteremia [6, 13, 21], and all ED patients aged ≥15 years who received a diagnosis of MRSA bacteremia from 1 January 2001 through 31 December 2010 were recruited. For patients with repeated MRSA bacteremia during the study period, only the first episode was included, to ensure the statistical independence of the outcome analysis. MRSA bacteremia patients were then excluded if the bloodstream isolate was (1) not available or not typable by molecular analysis, (2) from a patient without prior healthcare-associated exposure within the past 1 year, or (3) from a patient who was not followed for ≥30 days after the index hospital discharge. Therefore, only nonduplicate, community-onset, healthcare-associated MRSA bacteremia patients with available bloodstream isolates and evaluable outcomes entered the final analysis. This study was approved by the institutional review board of the hospital, and the requirement for informed consent from each patient was waived.

**Data Collection and Information on Variables**

The patient data included demographic characteristics, history of healthcare-associated exposure within the past 1 year, pre-existing comorbidities, initial ED presentations, and type of empirical antimicrobial therapy. The index hospitalization course, definitive antimicrobial therapy, vancomycin trough level (if available), focus of bacteremia, hospitalization length, and all-cause mortality were recorded from the medical records. The survival status and occurrence of recurrent MRSA bacteremia after the index hospitalization were assessed from the hospital’s outpatient department records and the laboratory computer database.

The epidemiological definition of healthcare-associated exposure included the following characteristics: (1) long-term care facility or nursing home residence; (2) receipt of hemodialysis, intravenous chemotherapy or antibiotics, or a transfusion or surgical procedure in an outpatient setting; (3) receipt of parenteral nutrition at home; (4) prior hospitalization for >2 days; and (5) use of long-term venous access devices, urinary catheters, or other percutaneous devices. MRSA isolates from patients with a healthcare-associated exposure history were defined as healthcare-associated MRSA. MRSA isolates from patients without healthcare-associated exposure within the past 1 year were defined as community-acquired
MRSA [6, 13] and were excluded from the outcome analysis. Severity of preexisting comorbidities was assessed using the modified Charlson comorbidity score [22]. Initial vital signs on ED presentation were classified according to the International Sepsis Definitions. Bandemia was defined as band-form cells exceeding 10% of the white blood cell population, and thrombocytopenia was defined as a platelet count <100 000 platelets/mm³, as determined by complete blood cell count. Acute severity of bacteremia as assessed by the sepsis syndrome criteria was graded as follows: no sepsis or simple sepsis, severe sepsis, and septic shock [14, 23]. The diagnosis of infection focus was based on clinical, laboratory, radiographic, and associated microbiological investigations. Primary bacteremia was diagnosed if no infection focus could be identified at the time of hospital discharge, after an extensive sepsis work-up.

During the study period, glycopeptides (either vancomycin or teicoplanin) were the suggested initial antibiotics for MRSA treatment. However, early empirical glycopeptide treatment was not encouraged at our hospital [24]. Linezolid and daptomycin were used at the discretion of the infectious disease physicians. Effective antibiotics for MRSA bacteremia were defined as intravenous glycopeptides, linezolid, or daptomycin [25]. Effective empirical antibiotic treatment was defined as the initiation of anti-MRSA antibiotics within 24 hours of obtaining the index blood culture. Inadequate vancomycin therapy was defined as a vancomycin trough level of <10 mg/L measured after ≥3 days of vancomycin therapy.

Antimicrobial Susceptibility Testing and Molecular Analysis

Blood culture specimens were inoculated into BACTEC standard culture bottles or BACTEC PLUS culture bottles in a BACTEC 9000 system (Becton Dickinson, Sparks, MD). S. aureus was identified by colony morphology, Gram-staining results, and a positive result of a slide or tube coagulase test. Initial antimicrobial susceptibility was determined by the standard disk-diffusion method. A 30-μg cefoxitin disk (BBL Microbiology Systems, Cockeysville, MD) was used to detect MRSA after 2006 [26, 27]. Clinical MRSA isolates were collected and stored at −70°C in trypticase soy broth (Difco Laboratories, Detroit, MI) supplemented with 15% glycerol. The MICs of vancomycin, oxacillin, ampicillin-sulbactam, ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole, erythromycin, clindamycin, and doxycycline were determined for all available MRSA isolates, using the agar-dilution method recommended by the Clinical and Laboratory Standards Institute [28]. The SCCmec elements (I–V) and mecA gene were identified as previously described [29, 30]. The presence of Panton-Valentine leukocidin genes lukF and lukS was investigated by the polymerase chain reaction technique, using the primer described previously [31].

Study Group Classification and Outcome Determination

All patients enrolled in the final outcome analysis were, on the basis of their epidemiological backgrounds, determined as having healthcare-associated MRSA bacteremia. They were then subcategorized according to their molecular typing and vancomycin MIC results. CA-MRSA isolates were defined as those with molecular typing results of SCCmec type IV or V. MRSA isolates with SCCmec type I, II, or III were defined as hospital-associated MRSA (HA-MRSA) [32, 33]. Finally, the CA-MRSA and HA-MRSA bacteremia groups were further classified into subgroups with low (≤1 μg/mL) or high (>2 μg/mL) vancomycin MICs.

The primary study outcome was treatment failure, which was defined in terms of the following events: (1) all-cause 30-day mortality; (2) persistent bacteremia, defined as a positive blood culture for MRSA obtained after >7 days of anti-MRSA antibiotic treatment during the index hospitalization; or (3) recurrent MRSA bacteremia within 30 days of discontinuation of anti-MRSA therapy [34–36]. The length of hospital stay and requirement for intensive care unit admission during the index hospitalization were evaluated as secondary study outcomes.

Statistical Analysis

All MRSA bacteremia patients finally enrolled in this study were classified as belonging to the low-vancomycin-MIC CA-MRSA, high-vancomycin-MIC CA-MRSA, low-vancomycin-MIC HA-MRSA, and high-vancomycin-MIC HA-MRSA groups according to their antimicrobial susceptibility testing and molecular typing results. Binary variables were compared by the χ² test. The age, Charlson comorbidity score, and duration of hospitalization of each study group were compared by 1-way analysis of variance. The Charlson comorbidity score was dichotomized at the mean value for regression modeling and stratified analysis. Backward stepwise and manual multivariate logistic regression modeling was performed to determine the independent predictors of treatment failure. Variables associated with mortality at P values of ≤.20 in univariate analyses were included in the multivariate model. In addition, we performed stratified analysis by Charlson comorbidity score and repeated multivariate logistic regression modeling to lessen the confounding effect of the severity of preexisting disease. Data were analyzed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All P values are 2-sided, and a P value of <.05 was considered statistically significant.

RESULTS

A total of 346 nonduplicate community-onset MRSA bacteremia episodes with available MRSA isolates recorded from 1 January 2001 through 31 December 2010 were initially recruited for this study. Forty-seven episodes were identified as
community-acquired MRSA bacteremia and were therefore excluded from outcome analysis. Molecular analysis showed that 45 (95.7%) of the community-acquired MRSA bacteremia isolates were SCCmec type IV or V MRSA. Of the remaining 299 episodes of healthcare-associated MRSA bacteremia, 8 were excluded because of incomplete posthospitalization follow-up. A total of 291 healthcare-associated MRSA bacteremia episodes were finally enrolled and divided into the following 4 study groups, as described in the Methods section: low-vancomycin-MIC CA-MRSA (n = 111), high-vancomycin-MIC CA-MRSA (n = 6), low-vancomycin-MIC HA-MRSA (n = 127), and high-vancomycin-MIC HA-MRSA groups (n = 47). Among all healthcare-associated MRSA isolates, the SCCmec type I/II/III (ie, HA-MRSA) isolates were significantly more likely than the SCCmec type IV/V (ie, CA-MRSA) isolates to have vancomycin MICs of ≥2 μg/mL (27.0% vs 5.1%, P < .001).

Clinical Features and Outcomes

The clinical characteristics of the 291 study patients are shown in Table 1. Patients with low-vancomycin-MIC CA-MRSA infection were relatively young and had lower percentages of prior hospitalization, end-stage renal disease, and high Charlson comorbidity score (≥4). Patients with high-vancomycin-MIC HA-MRSA bacteremia had a higher percentage of end-stage renal disease, a high Charlson comorbidity score, and severe sepsis or septic shock status on initial presentation. The effective empirical antibiotics, definitive antibiotic treatment, inadequate vancomycin therapy, infection focus, and time to removal of infected vascular device parameters did not differ significantly among the 4 study groups. Patients with low-vancomycin-MIC CA-MRSA bacteremia had the lowest overall treatment failure rate among the 4 study groups (P = .013; Figure 1).

Strain-Specific Risk for Treatment Failure

To evaluate whether CA-MRSA has a different clinical impact than HA-MRSA on patient outcomes, treatment failure risk between the 117 CA-MRSA and 174 HA-MRSA bacteremia patients was first analyzed. Multivariate logistic regression analysis revealed that HA-MRSA infection had a significantly higher treatment failure risk than CA-MRSA infection (adjusted odds ratio [aOR], 1.988; 95% confidence interval [CI], 1.131–3.496) after adjustment for other independent confounders, including high Charlson comorbidity score (≥4; aOR, 2.140; 95% CI, 1.198–3.822), thrombocytopenia (aOR, 2.074; 95% CI, 1.038–4.143), severe sepsis (aOR, 3.766; 95% CI, 1.989–7.131), septic shock (aOR, 7.815; 95% CI, 3.619–16.877), and endovascular infection (aOR, 2.434; 95% CI, 1.121–5.288).

We further explored whether the vancomycin susceptibility difference of between CA-MRSA and HA-MRSA accounted for their disparity in clinical impact on bacteremia patients. Because only 6 CA-MRSA isolates with high vancomycin MICs (≥2 μg/mL) were identified, this group was excluded from subsequent analysis because of the difficulty in reaching statistical significance. Therefore, only the outcomes of the 2 HA-MRSA bacteremia groups were compared with those of the low-vancomycin-MIC CA-MRSA bacteremia group. The multivariate logistic regression model that controlled for all potential confounding variables revealed that the risk for treatment failure was higher for both low- and high-vancomycin-MIC HA-MRSA bacteremia patients than for low-vancomycin-MIC CA-MRSA bacteremia patients (aORs, 1.853 [95% CI, 1.006–3.413] for low-vancomycin-MIC HA-MRSA and 2.393 [95% CI, 1.079–5.309] for high-vancomycin-MIC HA-MRSA). In the Charlson comorbidity score-stratified analysis, the differences in the risk of treatment failure between the HA-MRSA bacteremia patients and the CA-MRSA bacteremia patients remained statistically significant among patients with a high Charlson comorbidity score (aORs, 2.595 [95% CI, 1.164–5.786] and 3.191 [95% CI, 1.180–8.635], respectively; Table 2).

DISCUSSION

In the current study, we specifically evaluated the impact of different MRSA strains (CA-MRSA vs traditional hospital-associated MRSA) on bacteremic patients and clarified whether the outcome differences resulted from different vancomycin MICs. We found that CA-MRSA strains were associated with lower rates of treatment failure than traditional hospital-associated MRSA strains. However, the effect of MRSA strain was independent of the difference in vancomycin MIC, suggesting the possibility of strain-specific virulence factor effect. Although CA-MRSA was associated with better clinical outcomes than traditional hospital-associated MRSA, the additional disease burden imposed by the spread of CA-MRSA in the community and the presence of high-vancomycin-MIC CA-MRSA isolates indicate the importance of ongoing monitoring of the impact of CA-MRSA at the population and individual levels.

The wide spread of CA-MRSA in both community and hospital environments makes the possibility that CA-MRSA could cause more-severe disease and worse clinical outcomes than traditional hospital-associated MRSA a serious concern. In the setting of community-onset infections, CA-MRSA infection often occurs in patients with less comorbid illness than associated with infection due to traditional hospital-associated MRSA. Studies addressing the relative virulence between CA-MRSA and HA-MRSA, therefore, have often
Table 1. Clinical Data of 291 Patients With Healthcare-Associated Methicillin-Resistant *Staphylococcus aureus* Bacteremia, by Isolate Genotype and Minimum Inhibitory Concentration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CA-MRSA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HA-MRSA&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC ≤ 1 μg/mL (n = 111)</td>
<td>MIC ≥ 2 μg/mL (n = 6)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>64.9 ± 16.3</td>
<td>70.8 ± 14.9</td>
<td></td>
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<tr>
<td>Male sex</td>
<td>65 (58.6)</td>
<td>5 (83.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 (59.1)</td>
<td>32 (68.1)</td>
<td></td>
</tr>
<tr>
<td>Type of healthcare exposure&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTCF residence</td>
<td>20 (18.0)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>OPD invasive procedure&lt;sup&gt;d&lt;/sup&gt;</td>
<td>38 (34.2)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Prior hospitalization</td>
<td>94 (84.7)</td>
<td>6 (100.0)</td>
<td></td>
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<tr>
<td>Comorbid medical condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (33.3)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>36 (32.4)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>22 (19.8)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>10 (9.0)</td>
<td>1 (16.7)</td>
<td></td>
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<tr>
<td>Congestive heart failure</td>
<td>9 (8.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>24 (21.6)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>17 (15.3)</td>
<td>1 (16.7)</td>
<td></td>
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<tr>
<td>Charlson comorbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.7 ± 2.6</td>
<td>7.0 ± 3.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High (≥4)</td>
<td>52 (46.8)</td>
<td>5 (83.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Initial presentation</td>
<td></td>
<td></td>
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<tr>
<td>Bandemia (&gt;10%)</td>
<td>18 (16.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22 (19.8)</td>
<td>1 (16.7)</td>
<td></td>
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<tr>
<td>Sepsis severity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sepsis/no SIRS</td>
<td>70 (63.1)</td>
<td>4 (66.7)</td>
<td></td>
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<tr>
<td>Severe sepsis</td>
<td>25 (22.5)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>16 (14.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Effective empirical antibiotics&lt;sup&gt;e&lt;/sup&gt;</td>
<td>24 (21.6)</td>
<td>3 (50.0)</td>
<td></td>
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<tr>
<td>Definitive effective antibiotics&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (4.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>85 (78.6)</td>
<td>6 (100.0)</td>
<td></td>
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<tr>
<td>Other anti-MRSA agents&lt;sup&gt;g&lt;/sup&gt;</td>
<td>8 (8.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Inadequate vancomycin therapy&lt;sup&gt;h&lt;/sup&gt;</td>
<td>25 (23.9)</td>
<td>3 (60.0)</td>
<td></td>
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<tr>
<td>Infection focus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin and soft tissue</td>
<td>23 (20.7)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Vascular device-related</td>
<td>22 (19.8)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Low respiratory tract infection</td>
<td>21 (18.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Endovascular infection</td>
<td>17 (15.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Orthopedic infection</td>
<td>10 (9.0)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Other infection site</td>
<td>12 (10.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Presence of PVL gene</td>
<td>29 (26.1)</td>
<td>1 (16.7)</td>
<td></td>
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<tr>
<td>Hospitalization length, days</td>
<td>30.3 ± 27.5</td>
<td>37.2 ± 11.5</td>
<td></td>
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</table>

<sup>a</sup> CA-MRSA: Community-associated methicillin-resistant *Staphylococcus aureus*.<br><sup>b</sup> HA-MRSA: Healthcare-associated methicillin-resistant *Staphylococcus aureus*.<br><sup>c</sup> Type of healthcare exposure: LTCF residence = long-term care facility residence; OPD invasive procedure = outpatient invasive procedure.<br><sup>d</sup> OPD invasive procedure: OPD = outpatient department; invasive procedure = invasive procedure performed in the ambulatory setting.<br><sup>e</sup> Effective empirical antibiotics: 1st-line antibiotics effective against MRSA (<8 μg/mL).<br><sup>f</sup> Definitive effective antibiotics: 1st-line antibiotics effective against MRSA (≤1 μg/mL).<br><sup>g</sup> Other anti-MRSA agents: Other anti-MRSA agents include linezolid, daptomycin, and tigecycline.<br><sup>h</sup> Inadequate vancomycin therapy: Inadequate vancomycin therapy includes suboptimal vancomycin serum levels or prolonged duration of vancomycin therapy.<br><sup>i</sup> Skin and soft tissue: Skin and soft tissue infection includes cellulitis, abscess, and wound infection.<br><sup>j</sup> Vascular device-related: Vascular device-related infection includes infection at the site of a vascular catheter or vascular device.<br><sup>k</sup> Low respiratory tract infection: Low respiratory tract infection includes pneumonia and other infections of the lower respiratory tract.<br><sup>l</sup> Endovascular infection: Endovascular infection includes infection at the site of an endovascular device or catheter.<br><sup>m</sup> Orthopedic infection: Orthopedic infection includes infection at the site of an orthopedic implant or prosthesis.<br><sup>n</sup> Other infection site: Other infection site includes infection at any other site that is not skin and soft tissue, vascular device-related, low respiratory tract infection, endovascular infection, orthopedic infection, or other infection site.<br><sup>n</sup> No focus identified: No focus identified includes infection without a specific focus identified.<br><sup>o</sup> Time to remove infected vascular catheter: Time to remove infected vascular catheter is the interval from initiation of vancomycin therapy to removal of the infected vascular catheter.<br><sup>p</sup> Presence of PVL gene: Presence of PVL gene indicates the presence of the Panton-Valentine leukocidin (PVL) gene in the *Staphylococcus aureus* isolate.
been limited by small case numbers [10–14] or failure to control for potential confounding factors [10–12, 15, 16]. Lalani et al, who used data from 88 patients with MRSA endocarditis or bacteremia as part of a multinational randomized clinical trial, first reported that USA300 MRSA strains were associated with better clinical outcomes than other non-USA300 MRSA strains, suggesting less virulence of CA-MRSA than HA-MRSA. This study, however, only provided univariate comparison and was not able to control for potential confounders, because patients with USA300 MRSA infection were younger and had less comorbidity than patients with non-USA300 MRSA infection [10]. Although subsequent studies failed to show the outcome difference between CA-MRSA and HA-MRSA infections [11–14], a lower mortality rate among

![Figure 1](https://academic.oup.com/cid/article-abstract/55/10/1329/324390)  
**Figure 1.** Treatment outcomes of 291 patients with community-onset, healthcare-associated methicillin-resistant *Staphylococcus aureus* bacteremia, by genotype and vancomycin minimum inhibitory concentration. Number in parentheses denotes the patients with treatment failure in each study group. Abbreviations: CA, community-associated; HA, hospital-associated; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus.*

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**Table 1 continued.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CA-MRSA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HA-MRSA&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC ≤1 μg/mL (n = 111)</td>
<td>MIC ≥2 μg/mL (n = 6)</td>
</tr>
<tr>
<td>ICU admission required</td>
<td>28 (25.2)</td>
<td>2 (33.3)</td>
</tr>
</tbody>
</table>

Data are No. (%) of patients or mean value ± SD.

Abbreviations: CA, community associated; HA, hospital-associated; ICU, intensive care unit; LTCF, long-term care facility; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; OPD, outpatient department; PVL, Panton-Valentine leukocidin; SIRS, systemic inflammatory response syndrome.

<sup>a</sup> Refers to MRSA isolates with staphylococcal cassette chromosome *mec* types IV or V.

<sup>b</sup> Refers to MRSA isolates with staphylococcal cassette chromosome *mec* types I, II, or III.

<sup>c</sup> Within 1 year prior to the index blood culture.

<sup>d</sup> Includes chemotherapy, hemodialysis, home parenteral nutrition, transfusion, or surgery.

<sup>e</sup> Defined as the intravenous administration of vancomycin, teicoplanin, daptomycin, or linezolid within 24 hours of obtaining the index blood culture.

<sup>f</sup> Evaluated in 251 patients who survived >3 days after the index blood culture.

<sup>g</sup> Includes teicoplanin and linezolid.

<sup>h</sup> Defined as vancomycin trough level of <10 μg/mL measured after ≥3 days of vancomycin therapy.

<sup>i</sup> Vancomycin trough level was tested in 66 patients.

<sup>j</sup> Vancomycin trough level was tested in 5 patients.

<sup>k</sup> Vancomycin trough level was tested in 78 patients.

<sup<l> Vancomycin trough level was tested in 30 patients.

<sup>m</sup> Includes primary bacteremia and bacteremia with no identified focus because of a rapidly fatal course.

<sup>n</sup> Using first blood culture positive for MRSA as day 1.
patients with CA-MRSA infection, compared with patients with HA-MRSA infection, was observed across all these 4 studies. Two studies, on the contrary, showed that patients with USA300 MRSA bacteremia were associated with worse clinical outcomes than patients with non-USA300 MRSA bacteremia [15, 16]. However, these 2 studies were limited either by the failure of adjustment for potential confounding factors, such as inappropriate initial antimicrobial
therapy [15, 16], or by use of acute sepsis severity rather than mortality as the final study outcome [16]. Furthermore, although higher USA300 MRSA virulence was suggested in both studies, the crude mortality rate among patients with non-USA300 MRSA bacteremia was higher than among patients with USA300 MRSA bacteremia, irrespective of their lower initial sepsis severity.

More recently, studies have shown that USA300 MRSA infection was independently associated with a better treatment outcome than non-USA300 MRSA infection [17–19]. Our study, which used complete-cohort cases and strictly controlled for potential confounding factors, provides convincing supporting evidence for the association of CA-MRSA with better clinical outcomes than those for traditional hospital-associated MRSA. Exclusion of patients with community-acquired MRSA bacteremia and performance of stratified analysis in this study further reduced the influence of the severity of underlying comorbidity on study outcome and consolidated our study findings. Because the CA-MRSA strain pattern in Taiwan is distinct from that in the United States, the different impacts of community-associated and hospital-associated MRSA might be a universal rather than local phenomenon.

Compared with traditional hospital-associated MRSA, CA-MRSA carries different resistance genes and shows susceptibility to various non-β-lactam antibiotics [37]. It is therefore important to clarify the relationship between the disparate treatment outcomes of CA-MRSA and hospital-associated MRSA infections and their different antimicrobial susceptibilities. In this study, the MIC of vancomycin was lower for CA-MRSA than for hospital-associated MRSA. However, the different outcomes of CA-MRSA and traditional hospital-associated MRSA infection were independent of the vancomycin MIC status. It is supported by the observation that, given the same vancomycin MIC range, patients with low-vancomycin-MIC hospital-associated MRSA still had higher risk of treatment failure than patients with low-vancomycin-MIC CA-MRSA. One possible explanation for this novel finding is that different MRSA strains have different intrinsic virulence factors [37–40]. Our study therefore indicates that, in addition to early use of effective antibiotics, adjuvant therapy targeting these intrinsic virulence factors might offer additional therapeutic advantage for patients with MRSA infections.

This observational study had some limitations. First, this was a single-center study conducted in Taiwan. The extent to which our study findings can be generalized, especially to communities with different circulating CA-MRSA strains, requires further confirmation. Second, the clinical data on this observational cohort were retrospectively collected and are therefore subject to information bias. Finally, the high-vancomycin-MIC HA-MRSA group had a nonsignificantly higher odds of treatment failure, compared with the low-vancomycin-MIC HA-MRSA group. This could be due to case numbers that were insufficient to reach statistical significance in this study, rather than to a lack of impact of vancomycin MIC on patient outcomes.

In summary, among patients with community-onset and healthcare-associated MRSA bacteremia, CA-MRSA infection was associated with better treatment outcomes than traditional hospital-associated MRSA infection. The difference in clinical impact between CA-MRSA and traditional hospital-associated MRSA was independent of their vancomycin MICs. This hints at the necessity of identifying potential intrinsic virulence factors, in addition to determining the vancomycin MIC, to improve the treatment outcomes of patients with MRSA infection. Furthermore, the emergence of high-vancomycin-MIC CA-MRSA isolates highlights the importance of vigorous strategies to contain infection with and the spread of CA-MRSA.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


