Bone and joint infection as a predictor of community-acquired methicillin-resistant Staphylococcus aureus bacteraemia: a comparative cohort study

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Received 2 December 2013; returned 11 January 2014; revised 17 February 2014; accepted 1 March 2014

Background: A new clone of community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA), sequence type (ST) 72-staphylococcal chromosomal cassette mec (SCCmec) type IV/IVA without the Panton–Valentine leucocidin (PVL) genes, has been the major clonal type in Korea since 2007. However, there have been no evaluations of the clinical features, risk factors and outcomes associated with CA-MRSA bacteraemia in Korea.

Methods: Adult patients with community-acquired S. aureus bacteraemia (SAB) were enrolled between 1 January 2004 and 31 September 2012. We compared the clinical features and outcomes of CA-MRSA bacteraemia with those of community-acquired methicillin-susceptible S. aureus (CA-MSSA) bacteraemia and evaluated the risk factors for CA-MRSA infection. A microbiological study of the CA-MRSA isolates was also conducted.

Results: In total, 169 patients were included, i.e. 31 (18%) patients with CA-MRSA bacteraemia and 138 (82%) patients with CA-MSSA bacteraemia. Bone and joint infection [45.2% (14/31) versus 22.5% (31/138); adjusted OR, 2.61; 95% CI, 1.09–6.21] was an independent predictor of CA-MRSA bacteraemia. There were no significant differences in relapse of bacteraemia and mortality within 12 weeks after SAB between the two groups. ST72-SCCmec type IV/IVA without the PVL genes was the most common genotype, especially among bone and joint infections (64%, 9/14) as well as among the CA-MRSA isolates (71%, 22/31).

Conclusions: CA-MRSA accounted for 18% of community-acquired SAB and was significantly associated with bone and joint infection. Our study suggests that CA-MRSA should be considered in patients with bone and joint infection and that empirical therapy against MRSA should be included.

Keywords: sequence type, SCCmec, methicillin susceptible

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) has been identified as a nosocomial pathogen. However, since four paediatric deaths occurred in the USA due to severe MRSA infection without established risk factors for MRSA acquisition in 1999,1 community-acquired MRSA (CA-MRSA) infections have emerged worldwide.2 The global epidemiology of CA-MRSA is remarkably heterogeneous and the distribution of dominant CA-MRSA clones and the Panton–Valentine leucocidin (PVL) gene status vary among countries.1 Unlike hospital-acquired MRSA clones, which carry staphylococcal chromosomal cassette mec (SCCmec) type I, II or III, the CA-MRSA clones possess SCCmec type IV or V and frequently carry the PVL genes.1–5 Epidemiological studies of CA-MRSA in Korea found that the predominant clonal type was a new clone of CA-MRSA, a sequence type (ST) 72-SCCmec type IV/IVA without PVL, which was initially discovered in 2007. This is a genetically distinct strain compared with other clones with international distributions.5 However, most previous studies examining this clonal type included both pathogens and colonizers and CA-MRSA isolates that cause invasive infections, such as bacteraemia, were rare.

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CA-MRSA has become widely endemic in many places; therefore, distinguishing CA-MRSA from community-acquired methicillin-susceptible *S. aureus* (CA-MSSA) in patients with suspected *S. aureus* bacteraemia (SAB) is now an important clinical challenge. A previous prospective study showed that clinical and epidemiological risk factors are not reliable for distinguishing between MRSA and MSSA. However, most of these patients (89%) had skin or soft tissue infections and the major CA-MRSA strain was ST8/USA300.

A very limited number of studies have compared CA-MRSA bacteraemia and CA-MSSA bacteraemia. Furthermore, the new CA-MRSA clone in Korea may have different clinical characteristics compared with those from other countries. Thus, we conducted a comparative cohort study to identify representative CA-MRSA clones in community-acquired SAB and to evaluate the clinical features, risk factors and outcomes of CA-MRSA bacteraemia compared with CA-MSSA bacteraemia.

**Methods**

**Study design and patient selection**

This study was conducted at Asan Medical Center, a 2700 bed general hospital that provides both primary and tertiary care throughout Korea. Adult patients aged ≥16 years with SAB were enrolled and followed up by the study protocol over a 12 week period between 1 January 2004 and 31 September 2012. Retrospective SAB data from 1 January 2004 to 31 July 2008 were included to increase the statistical power of the analysis.

Community-acquired bacteraemia was defined based on a positive culture obtained from a patient within 48 h of admission if the patient did not satisfy the following criteria for healthcare-associated bacteraemia: received intravenous therapy at home or in an outpatient clinic during the previous 30 days; received renal dialysis in a hospital or clinic during the previous 30 days; or had been hospitalized for ≥2 days in the previous 90 days; or resided in a nursing home or long-term care facility for ≥2 days during the previous 90 days. A positive culture from a patient who had been hospitalized for ≥48 h was considered to be hospital acquired.

Patients were excluded from this study if they had polymicrobial bacteraemia. Only the first episode of SAB in each patient was included in the analysis. This study was approved by the Asan Medical Center Institutional Review Board, who waived formal informed consent in view of the observational nature of the study.

**Data collection**

Demographic characteristics, laboratory results, underlying diseases or conditions, presence or absence of medical devices, site of infection, antibiogram results, patient management and clinical outcomes were evaluated. The system of McCabe and Jackson was used to classify the severity of the underlying disease. The Charlson comorbidity index was used to produce a composite score of comorbid conditions. The site of infection was determined based on clinical, radiological and bacteriological investigations. Bacteraemia without an identifiable site of infection was classified as primary bacteraemia. Appropriate empirical antibiotic therapy was defined as the use of an antimicrobial agent with activity against the organism on the day of or 1 day after the index blood culture.

**Microbiological data**

All of the *S. aureus* isolates were identified using standard methods. Antimicrobial susceptibilities were determined using the MicroScan system (Dade Behring, West Sacramento, CA, USA) and the standard criteria of the CLSI.

Isolates were classified as multidrug resistant if they were resistant to three or more different classes of antibiotics (excluding β-lactams). Methicillin resistance was confirmed by PCR detection of the *meCA* gene. The presence of the PVL genes, the SCCmec type and the multilocus sequence type (MLST) were determined using previously described methods.

The presence of 41 putative virulence genes was determined using available CA-MRSA isolates.

**Statistical analyses**

The demographic distributions and clinical features of patients with CA-MRSA bacteraemia and CA-MSSA bacteraemia were compared. Categorical variables were analysed using the χ² test or Fisher’s exact test, as appropriate. Normally and non-normally distributed continuous variables were analysed using Student’s *t*-test and the Mann–Whitney *U*-test, respectively. The risk factors related to CA-MRSA bacteraemia were assessed using univariate and multivariate logistical regression analyses. All variables with *P* < 0.2 in the univariate analysis and other variables of clinical importance were included in the multiple logistic regression model. Tests for interactions and collinearity among variables were conducted. The final model was constructed using the stepwise selection procedure. *P* < 0.05 was considered statistically significant. The data were analysed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Study population**

In total, 169 non-duplicated episodes of SAB satisfied the definition of community-acquired SAB during the study period and were included in the final analysis. Of these, 31 patients (18%) had CA-MRSA bacteraemia and 138 patients (82%) had CA-MSSA bacteraemia.

**Demographic and clinical characteristics**

The median age of patients with community-acquired SAB was 61 years (IQR, 51.5–68.5 years) and 102 (60.4%) were male patients. Table 1 shows a comparison of the demographic and clinical characteristics of the patients with CA-MRSA bacteraemia and those with CA-MSSA bacteraemia. Baseline characteristics were similar in the two groups. However, CA-MRSA bacteraemia was significantly associated with bone and joint infection (*P* = 0.01) and most cases were vertebral osteomyelitis (78.6%, 11/14).

**Risk factors for CA-MRSA bacteraemia**

The univariate analysis indicated that bone and joint infection was a significant risk factor for CA-MRSA bacteraemia. The results of the multivariate analysis showed that CA-MRSA bacteraemia was independently associated with bone and joint infection (45.2% [14/31] versus 22.5% [31/138]); adjusted OR, 2.61; 95% CI, 1.09–6.21; *P* = 0.03).

**Treatment and outcome**

Table 2 shows a comparison of the treatments and outcomes for patients with CA-MRSA bacteraemia and those with CA-MSSA bacteraemia. The CA-MRSA group was significantly more likely to receive inappropriate empirical antibiotic therapy than the CA-MSSA group (*P* < 0.001). Persistent bacteraemia was also
observed more frequently in the CA-MRSA group \((P<0.001)\) and the CA-MRSA group was significantly associated with longer hospital stays than the CA-MSSA group \((P=0.004)\). However, there were no significant differences in relapse of bacteraemia within 12 weeks after SAB and the crude mortality and SAB-attributable mortality at 1 week, 30 days and 12 weeks in the two groups.

**Molecular characteristics and antimicrobial susceptibility of CA-MRSA isolates**

The microbiological characteristics of the CA-MRSA isolates are summarized in Table 3. The most common SCCmec type was type IV/IVA \((74.2\%, 23/31)\) and type IVA was dominant among these isolates \((73.9\%, 17/23)\). The PVL genes were negative in all CA-MRSA isolates, except for two isolates that carried SCCmec type I. The most prevalent ST was ST72 \((71.0\%)\). Among the various genotypes assigned based on the SCCmec types and STs, ST72-SCCmec type IVA was the most common \((71\%, 22/31)\). The frequency of this genotype among bone and joint infections and vertebral osteomyelitis in particular was 64\% \((9/14)\) and 64\% \((7/11)\), respectively. Antimicrobial susceptibility tests using seven non-β-lactam antimicrobial agents found that 81.8\% \((18/22)\) of the ST72-SCCmec type IVA CA-MRSA isolates were not multidrug resistant. The overall vancomycin MIC distribution was as follows: MIC of \(\leq 1.0\) mg/L, 20 isolates \((64.5\%); \) and MIC of 1.5 mg/L, 11 isolates \((35.5\%).\) No isolates had a vancomycin MIC of \(\geq 2\) mg/L. The presence of 41 putative virulence genes in the 11 available ST72-SCCmec type IVA CA-MRSA isolates is shown in Table S1 (available as Supplementary data at JAC Online).

**Discussion**

In the present study, it was interesting that bone and joint infection was an independent risk factor for CA-MRSA bacteraemia. Previous studies have suggested that bone and joint infections, especially osteomyelitis, only account for a minority of all CA-MRSA infections,\(^{19-21}\) which have been described widely in paediatric age groups.\(^{22,23}\) Dhanoa et al.\(^{24}\) reported that a database search detected only eight cases of acute osteomyelitis caused by CA-MRSA in adults.
The factors that contributed to the predominance of bone and joint infections in patients with CA-MRSA bacteraemia in the present cohort-based study are not clear. According to a study by Park et al., ST72-SCCmec IV/IVA is responsible for the increased rates of MRSA infection in haematogenous vertebral osteomyelitis in Korea. This and the present study suggest that ST72-SCCmec IV/IVA may have a possible role in the predominance of bone and joint infections in patients with CA-MRSA bacteraemia.

Cassat et al. performed an experimental study and showed that phenol-soluble modulins (PSMs), which are peptide toxins produced by CA-MRSA, are important virulence factors in the pathogenesis of S. aureus-induced bone destruction. This suggests that the expression of PSMs may have been enhanced in our CA-MRSA isolates, which requires further investigation.

A number of clinical studies based on mortality rates have indicated that MRSA strains are more virulent than MSSA strains, although there have been conflicting results. However, the present study showed contradictory results. There are several possible explanations. First, in terms of the baseline characteristics, the present study detected no significant differences between the two groups. Second, this may have been due partly to the lower virulence of SCCmec IV/IVA compared with other SCCmec types. Third, the relatively lower mortality risk associated with bone and joint infections may have contributed to the lack of difference in mortality between the two groups.

Interestingly, the rate of persistent bacteraemia (48.4%) in the present study was much higher than previously reported rates (6%–38%) in SAB. This may have been because the limited bactericidal activity and poor bone penetration of vancomycin reduced the clinical efficacy. ST72-SCCmec type-associated factors may also have played a role in the increased rate of persistent bacteraemia. However, a previous study reported that persistent bacteraemia was similar in all SCCmec types.

The present study showed that ST72-SCCmec type IV/IVA without the PVL genes was the main CA-MRSA clone in

### Table 2. Comparison of treatments and outcomes for patients with CA-MRSA and CA-MSSA bacteraemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CA-MRSA (n = 31)</th>
<th>CA-MSSA (n = 138)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate empirical antibiotic therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26 (83.9)</td>
<td>4 (2.9)</td>
<td>174.20 (43.81–692.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Persistent bacteraemia (≥7 days)</td>
<td>15 (48.4)</td>
<td>17 (12.3)</td>
<td>6.67 (2.80–15.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital stay (days), median (IQR)</td>
<td>47 (19–87)</td>
<td>24 (14–44.5)</td>
<td>NA</td>
<td>0.004</td>
</tr>
<tr>
<td>relapse of bacteraemia within 12 weeks&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/25 (4)</td>
<td>2/110 (1.8)</td>
<td>2.25 (0.20–25.84)</td>
<td>0.46</td>
</tr>
<tr>
<td>overall death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week mortality</td>
<td>1 (3.2)</td>
<td>5 (3.6)</td>
<td>0.89 (0.10–7.87)</td>
<td>0.99</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>2 (6.5)</td>
<td>19 (13.8)</td>
<td>0.43 (0.10–1.96)</td>
<td>0.37</td>
</tr>
<tr>
<td>12 week mortality</td>
<td>5 (16.1)</td>
<td>27 (19.6)</td>
<td>0.79 (0.28–2.25)</td>
<td>0.66</td>
</tr>
<tr>
<td>SAB-related death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week mortality</td>
<td>0 (0)</td>
<td>5 (3.6)</td>
<td>NA</td>
<td>0.59</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>1 (3.2)</td>
<td>13 (9.4)</td>
<td>0.32 (0.04–2.55)</td>
<td>0.47</td>
</tr>
<tr>
<td>12 week mortality</td>
<td>2 (6.5)</td>
<td>18 (13.0)</td>
<td>0.46 (0.10–2.09)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

<sup>a</sup>Once antimicrobial susceptibilities became available, the treatment regimen was adjusted accordingly (e.g. vancomycin (93.5%) or teicoplanin (6.5%) for CA-MRSA bacteraemia and nafcillin (63.9%) or cefazolin (36.1%) for CA-MSSA bacteraemia).

<sup>b</sup>Relapse of bacteraemia within 12 weeks after the day of index blood culture. Thirty-two patients (5 with CA-MRSA and 27 with CA-MSSA) and 2 patients (1 with CA-MRSA and 1 with CA-MSSA) were excluded from the analysis due to death and loss to follow-up, respectively.

### Table 3. Microbiological characteristics of CA-MRSA isolates

<table>
<thead>
<tr>
<th></th>
<th>SCCmec</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>type IV/IVA</td>
<td>type I</td>
<td>type II</td>
<td>type III</td>
</tr>
<tr>
<td></td>
<td>(n = 23)</td>
<td>(n = 2)</td>
<td>(n = 3)</td>
<td>(n = 3)</td>
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<tr>
<td>MLST</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ST72</td>
<td>22 (95.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>other STs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ST5</td>
<td>1 (4.3)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ST6</td>
<td>2 (66.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST8</td>
<td>1 (33.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST239</td>
<td>3 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST254</td>
<td>1 (50)</td>
<td></td>
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<tr>
<td>PVL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>positive</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>negative</td>
<td>23 (100)</td>
<td></td>
<td></td>
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<tr>
<td>Vancomycin MIC&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>≤1.0 mg/L</td>
<td>14 (60.9)</td>
<td>2 (100)</td>
<td>2 (66.7)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>1.5 mg/L</td>
<td>9 (39.1)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>≥2.0 mg/L</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are no. (%) of patients.

<sup>a</sup>Determined by broth microdilution, according to CLSI guidelines.
community-acquired SAB in Korea, which is compatible with previous studies. ST72 MRSA isolates have only rarely been reported in countries other than Korea and the isolates reported in other countries were sporadic. It seems that ST72 MRSA isolates are mainly circulating in Korea and they are the major pathogen that causes CA-MRSA bacteremia. In contrast to PVL-positive CA-MRSA isolates in Western countries, none of the ST72 SCCmec type IV/IVA CA-MRSA isolates carried the PVL genes.

The present study had several limitations. First, some retrospective data were included, so healthcare-associated risk factors might have been missed, thereby leading to the misclassification of healthcare-associated SAB as community-acquired SAB. However, analysis of the prospective data alone (22 CA-MRSA and 73 CA-MSSA bacteremia cases) showed that bone and joint infection was significantly associated with CA-MRSA bacteremia ($P=0.04$) in the univariate analysis and marginally associated with CA-MRSA bacteremia ($P=0.06$) in the multivariate analysis. A small sample size might have contributed to statistical insignificance in the multivariate analysis. Second, the present study was performed in a single hospital; therefore, there might have been discrepancies between the results of this study and the actual characteristics of CA-MRSA in Korea. To overcome these drawbacks, a multicentre prospective study with a larger number of cases should be performed.

In conclusion, CA-MRSA accounted for 18% of community-acquired SAB in the present Korean cohort and was significantly associated with bone and joint infections. ST72-SCCmec type IV/IVA without the PVL genes was the major clonal type among the CA-MRSA isolates. The results of the present study suggest that CA-MRSA should be considered in patients with bone and joint infections and that empirical therapy against MRSA should be included.

**Funding**

This research was supported by grants from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (grant numbers: HI12C08720000 and HI12C08720100).

**Transparency declarations**

None to declare.

**Supplementary data**

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

**References**

CA-MRSA and bone and joint infection