Role of SCCmec Type in Outcome of Staphylococcus aureus Bacteremia in a Single Medical Center

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Staphylococcus aureus virulence factors may determine infection presentation. Whether SCCmec type-associated factors play a role in S. aureus bacteremia is unclear. We conducted a prospective observation of adult inpatients with S. aureus bacteremia (1 November 2005 to 31 December 2006), performed SCCmec typing of methicillin-resistant S. aureus (MRSA) isolates, and stratified the results according to SCCmec type. We studied 253 patients. MRSA accounted for 163 (64.4%) cases. The illness severity index was similar in MRSA and methicillin-sensitive S. aureus (MSSA) cases. MRSA caused higher in-hospital mortality (23.9% versus 8.9%; P = 0.003), longer bacteremia (4.7 ± 6.5 days versus 2.7 ± 2.9 days; P = 0.01), but similar metastatic infection (14.7% versus 15.6%). Stratifying the results according to SCCmec type revealed significant differences. SCCmec type II caused highest mortality (33.3%) versus SCCmec IVa (13.5%), other MRSA (12.5%), and MSSA (9.9%). SCCmec IVa produced the highest metastatic infection (26.9% versus 9.1% [SCCmec II], 8.3% [other MRSA], and 15.6% [MSSA]). Persistent bacteremia (≥7 days) was similar in all SCCmec types (16.7 to 20.7%); each exceeded MSSA (6.7%; P = 0.05). In multivariate analysis, SCCmec II was a predictor of mortality (odds ratio [OR] = 3.73; 95% confidence interval [CI] = 1.81 to 7.66; P = 0.009), SCCmec IVa was a predictor of metastatic infection (OR = 3.52; CI = 1.50 to 8.23; P = 0.004), and MRSA (independent of SCCmec type) was a predictor of persistent bacteremia (OR = 4.16; CI = 1.47 to 11.73; P = 0.007). These findings suggest that SCCmec-associated virulence factors play a role in the outcome of S. aureus bacteremia. Additional studies are needed to identify which virulence factors are the determinants of increased mortality with SCCmec type II and metastatic infection with SCCmec type IVa.

We prospectively monitored all patients with S. aureus bacteremia admitted to our hospital, performed SCCmec typing of all MRSA isolates, and stratified patient clinical characteristics and outcome according to methicillin susceptibility and SCCmec type.

MATERIALS AND METHODS

The present study was conducted at a 600-bed teaching hospital in the Detroit area. It was approved by our Institutional Review Board (expedited review); the patient informed consent form was waived.

Blood culture results were reviewed daily (Monday to Friday) from 1 November 2005 to 31 December 2006. All adult (≥18-year-old) inpatients with one or more positive blood cultures for S. aureus were identified and monitored prospectively. They were evaluated within 24 h of notification and every 1 to 3 days afterward. Inclusion criteria included ≥1 positive blood culture for S. aureus with clinical signs of infection. Exclusions criteria included relapse (S. aureus infection with similar oxacillin susceptibility pattern in the preceding 3 months), initiating therapy prior to admission (transfer from other institutions), lack of signs of infection (considered to represent contamination), and death or withdrawal of care within 48 h of blood culture. Each patient was counted once. Demographics, clinical characteristics, implicated source, metastatic foci, therapy, and outcome were recorded. Illness severity index was calculated as suggested by Deyo et al. (7), based on the Charlson comorbidity index (4) and a modified acute physiology score (22). Echocardiograms were obtained at the discretion of the attending physicians. Blood cultures were generally repeated every 2 to 3 days until clearance.

Definitions. Bacteremia was defined as one or more positive blood cultures accompanied by systemic manifestations of infection such as fever, chills, and sweats, with or without local signs and symptoms. It was considered community-associated when it appeared within 48 h of admission without any healthcare risk factors (the presence of invasive device, history of surgery, hospitalization, dialysis, or residence in a long-term care facility within the preceding 12 months) or healthcare-associated (onset ≥48 h after admission or with ≥1 healthcare risk factor) as described by Kleves et al. (20). Duration of bacteremia was defined as the time from the first positive blood culture to the last negative blood culture.
TABLE 1. Characteristics of patients with S. aureus bacteremia according to methicillin susceptibility and SCC mec type

| Characteristic          | SCC mec type* | Control 1 (n = 47) | Control 2 (n = 50) | Control 3 (n = 49) | Control 4 (n = 49) | P       |
|------------------------|---------------|---------------------|---------------------|---------------------|---------------------|---------|
| Age (yr)*              | IVa (n = 52)  | 53.5 (20–91)        | 64.0 (21–88)        | 57.5 (25–87)        | 58.0 (22–90)        | 0.02    |
| No. female             |               | 25 (48.1)           | 45 (51.7)           | 9 (37.0)            | 43 (47.8)           | 0.7     |
| Race                   |               |                     |                     |                     |                     |         |
| Caucasians             | 13 (25.0)     | 40 (46.0)           | 5 (20.8)            | 32 (35.6)           | 0.1     |
| African-Americans      | 39 (75.0)     | 45 (51.7)           | 19 (79.2)           | 54 (60.0)           | 0.1     |
| Others                 | 0             | 2 (2.3)             | 1 (4.2)             | 11 (12.2)           | <0.001  |
| Diabetes               | 18 (34.6)     | 40 (46.0)           | 12 (50.0)           | 39 (43.2)           | 0.5     |
| Hemodialysis dependent | 6 (11.5)      | 18 (20.7)           | 11 (45.8)           | 35 (38.9)           | 0.005   |
| Cardiac disease        | 15 (28.8)     | 52 (59.8)           | 9 (37.5)            | 41 (45.6)           | 0.004   |
| Injection drug users   | 17 (32.7)     | 1 (1.1)             | 1 (4.2)             | 11 (12.2)           | <0.001  |
| Endovascular prosthesis| 7 (13.5)      | 16 (18.4)           | 6 (25.0)            | 16 (17.8)           | 0.7     |
| Community associated   | 27 (51.9)     | 19 (21.8)           | 5 (20.8)            | 24 (26.7)           | 0.001   |
| Illness severity index†| 2.7 ± 1.5     | 4.0 ± 1.3           | 3.4 ± 1.3           | 3.3 ± 1.2           | <0.001  |
| Source                 |               |                     |                     |                     |         |
| IVa                    | 10 (19.2)     | 21 (24.1)           | 8 (33.3)            | 24 (26.3)           | 0.6     |
| Endocarditis           | 3 (5.8)       | 3 (3.4)             | 0                   | 3 (3.3)             | 0.8     |
| Other endovascular tissues | 5 (9.6)  | 3 (3.4)             | 6 (25.0)            | 17 (18.9)           | 0.006   |
| Soft tissue            | 15 (28.8)     | 10 (11.5)           | 2 (8.3)             | 10 (11.1)           | 0.001   |
| Osteomyelitis          | 10 (19.2)     | 13 (14.9)           | 1 (4.2)             | 12 (13.3)           | 0.5     |
| Miscellaneous          | 4 (7.7)       | 15 (17.2)           | 4 (16.7)            | 9 (10.0)            | 0.1     |
| Unknown                | 5 (9.6)       | 21 (26.4)           | 3 (12.5)            | 17 (18.9)           | 0.04    |
| Removable focus        | 16 (30.8)     | 33 (37.9)           | 15 (62.5)           | 36 (40.0)           | 0.1     |
| Focus removed          | 15 (93.8)     | 32 (97.0)           | 14 (93.3)           | 36 (100.0)          | 0.7     |
| Days to removal*       | 1.5 (0–5)     | 3 (0–41)            | 2 (0–7)             | 2 (0–13)            | 0.2     |

* Results represent number (patients, days, etc.) with the percentage indicated in parentheses unless otherwise specified. * Median (range); † mean ± the standard deviation.

as the number of days between the first and last positive blood culture, as described previously (17). Patients who died within 4 days were assumed to have bacteremia until death and censored afterward. The duration in patients whose last culture was still positive was censored. The source of bacteremia was identified based on the presence of local signs and the isolation of S. aureus from the implicated source as previously described (17) and the Duke criteria for endocarditis (23). Metastatic infection was defined as a distant focus anatomically unrelated to the implicated source. Treatment was classified into vancomycin, β-lactams and miscellaneous. Patients were assigned to the vancomycin or nafcillin-cefazolin class if one of these agents was prescribed for >90% of the observed treatment days; otherwise, they were assigned to the miscellaneous group. The vancomycin dose was determined by the pharmacy dosing service to achieve a trough of 10 to 15 μg/ml. Vancomycin levels were drawn prior to the fourth dose, and the dose was adjusted accordingly if the level was ≤10 μg/ml. Nafcillin was dosed at 2 g every 4 h and cefazolin at 2 g every 8 h; the cefazolin dose was adjusted in case of renal failure. Outcomes included cure or death. Attributable mortality was defined as death with positive blood culture or persistent sepsis.

The results were stratified according to methicillin susceptibility, type of onset, and SCC mec type. All differences were statistically analyzed.

Microbiological methods. (i) Blood culture method. We used an automated continuous monitoring system, the BacT/Alert system (BioMerieux, Inc., Durham, NC). Positive bottles are examined by Gram staining and subcultured. Species identification and susceptibility tests are performed by using Staphaurex latex agglutination (Remel, Inc., Lenexa, KS) or the Vitek identification and susceptibility cards (bioMerieux Vitek, Inc., Hazelwood, MO).

(ii) DNA extraction. Frozen isolates were grown on Trypticase soy agar with 5% sheep blood (Remel) overnight at 35°C. One to three isolated colonies were suspended in 50 μl of sterile water and heated to 99°C for 15 min. Cellular debris was cleared by centrifugation at 16,000 × g for 1 min. DNA supernatant was stored at −20°C for use in each of the following procedures.

(iii) SCC mec typing by multiplex PCR. A master mix was prepared containing 18 primers (Applied Biosystems, Foster City, CA) targeting SCC mec types I, II, III, IVa, IVb, IVc, IVd, and V and the mecA gene (internal control); Platinum Taq DNA polymerase; deoxynucleoside triphosphates; MgCl₂; and PCR buffer (Invitrogen, Carlsbad, CA) as described by Zhang et al. (39). A total of 2 μl of extracted DNA was added to 48 μl of master mix and amplified according to instructions. Amplified product was separated by electrophoresis, stained, photographed, and analyzed on a Chemi-Imager 4000 (Alpha Innotech, San Leandro, CA). Positive and negative controls (four ATCC MRSA strains [BAA-39, BAA-41, BAA-42, and BAA-44] and four previously typed MRSA patient strains [CA60-1, CA85, T-127, and T-162]) were included in each PCR assay.

Statistical analysis. We used the chi-square test for categorical variables, a Student t test, or analysis of variance for continuous variables; the log-rank test for time-dependent variables; and stepwise forward logistic regression for multivariate analysis of dichotomous outcomes. All tests were performed using SPSS computer software release 10. A P value of <0.05 was considered to indicate statistical significance.

RESULTS

We encountered 287 patients with positive blood culture for S. aureus. Thirty-four of these individuals were excluded. Twenty-nine patients did not meet our inclusion criteria: recurrent disease (n = 7), death within 1 day of culture results (n = 7), transfer from or to other institutions (n = 7), no clinical signs of bacteremia (considered to have contamination; n = 5), and care withdrawn (n = 3). Five other patients were also excluded; three left against medical advice within 2 days of blood culture, and two did not have blood isolates saved. All remaining 253 patients were included. The median illness severity index was 3 (range, 0 to 8; 75th percentile = 4). MRSA accounted for 163 (64.4%) cases without significant difference in illness severity index (3.5 ± 1.5 [MRSA] versus 3.3 ± 1.2 [MSSA]). SCC mec typing revealed type II in 87 (53.4%) MRSA cases, type IVa in 52 (31.9%) MRSA cases, type IVc in 1 (0.6%) MRSA case, and nontypeable isolates in 23 (14.1%) MRSA cases. All 23 nontypeable isolates were PCR positive for mecA (internal control), but no amplifiable DNA targeted by Zhang multiplex primers was detected. No aberrant SCC mec type was encountered. Comparative patient characteristics are shown in Table 1. Patients with SCC mec type II
had higher illness severity scores. SCCmec type IVa was more common among drug users than among non-drug users (17/30 [56.7%] versus 35/223 [15.7%]; \( P = 0.001 \)) and among community-associated infections than among healthcare-associated infections (27/85 [36.0%] versus 26/178 [16.9%]; \( P = 0.001 \)). These isolates caused more often soft tissue infections or osteomyelitis. They were infrequent in patients with intravenous catheter (IVC)-associated bacteremia.

Treatment was principally beta-lactams for MSSA (80.0%) and vancomycin for MRSA (91.4%). The source was removable in 100 (39.5%) cases; it was removed in 97 cases (97.0%) within a median of 2 days (range, 0 to 41).

MRSA was associated with higher all-cause mortality (23.9% versus 8.9%; \( P = 0.003 \)), with a trend toward higher attributable mortality (7.4% versus 2.2%; \( P = 0.09 \)). These isolates were also associated with longer durations of bacteremia (4.7 \pm 6.5 versus 2.7 \pm 2.9 days; \( P = 0.01 \)) and persistence for \( \geq 7 \) days (19.6% versus 6.7%; \( P = 0.006 \)) but a comparable rate of metastatic infection (14.7% versus 15.6%).

Stratifying the results according to SCCmec type revealed significant differences. MRSA-associated increase in mortality was principally caused by SCCmec type II (Fig. 1). The mortality levels associated with SCCmec type IVa, other MRSA, and MSSA isolates were comparable, with each significantly lower than that observed with SCCmec type II. Stepwise forward logistic regression analysis of all relevant variables, including interaction between SCCmec type and illness severity index, revealed that SCCmec type II was an independent predictor of all cause and attributable mortality (Table 2). The SCCmec type illness severity index interaction did not meet regression model entry criteria. Other predictors of all cause mortality included hemodialysis dependence, age, endocarditis, and illness severity index. Other predictors of attributable mortality were metastatic infection and illness severity index.

With respect to the duration of bacteremia, 22.1% of the patients were still bacteremic at day 4 (11.5% in MSSA and 27.7% in MRSA). A Kaplan-Meier clearance curve showed significant differences (Fig. 2). Clearance was significantly slower for MRSA. The difference was more apparent between MSSA and SCCmec type II or type IVa. The difference between MSSA and other MRSA isolates did not reach statistical significance, probably due to the small number of other MRSA isolates. Multivariate analysis of all relevant variables, including interaction between oxacillin susceptibility and the day to removal of a removable focus, demonstrated that methicillin resistance, independent of the SCCmec type, was a predictor of persistence. Day to removal of a removable focus was dropped out. Other predictors included metastatic infections, having an endovascular prosthesis, and diabetes (Table 2).

The risk for metastatic infection was comparable in MSSA and all MRSA cases. However, stratifying the results according

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Outcome measure & Predictor & OR (95% CI) & \( P \) \\
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All cause mortality & Illness severity index & 2.78 (1.94–3.99) & <0.001 \\
& SCCmec type II & 3.73 (1.81–7.66) & 0.009 \\
& Hemodialysis & 7.24 (1.90–27.63) & 0.004 \\
& Age & 1.04 (1.01–1.07) & 0.004 \\
& Metastatic infection & 4.21 (1.16–15.34) & 0.029 \\
& Endocarditis & 10.71 (1.33–86.56) & 0.026 \\
Attributable mortality & Illness severity index & 1.77 (1.17–2.67) & 0.007 \\
& Metastatic infection & 7.89 (2.11–29.49) & 0.002 \\
& SCCmec type II & 4.97 (1.28–19.25) & 0.020 \\
Metastatic infection & Endocarditis & 30.82 (5.70–166.73) & <0.001 \\
& SCCmec type IVa & 3.52 (1.50–8.23) & 0.004 \\
& Hemodialysis & 2.71 (1.19–6.18) & 0.018 \\
Persistence (\( \geq 7 \) days) & Metastatic infection & 11.35 (4.24–31.43) & <0.001 \\
& Diabetes & 3.64 (1.45–9.15) & 0.006 \\
& MRSA & 4.16 (1.47–11.76) & 0.007 \\
& Prosthesis & 3.22 (1.30–8.00) & 0.012 \\
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\end{tabular}
\caption{Logistical regression analysis of predictors of outcome measures}
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\( \star \) OR, odds ratio; CI, confidence interval.
to SCCmec type revealed that type IVa was significantly more likely than SCCmec type II or other MRSA isolates to cause this complication; the difference with MSSA did not reach statistical significance (Fig. 3). Multivariate analysis, including the source of bacteremia and interaction between SCCmec type and all relevant variables, revealed that SCCmec type IVa was an independent predictor of metastatic infection (Table 2). SCCmec type IVa interaction with endocarditis or hemodialysis dependence did not meet model entry criteria.

**DISCUSSION**

*S. aureus* causes a wide spectrum of diseases ranging from mild to life-threatening (25, 27). Disease severity is determined by organism-related virulence factors and host condition (15, 18, 21, 37). *S. aureus* virulence factors are numerous and include surface proteins and toxins. They are regulated by multiple genes or gene groups (2, 11, 13, 24, 31). Several studies have shown that MRSA is associated with higher mortality (5, 32, 33, 38). Whether this is due to MRSA-associated virulence factors, resistance to antibiotics, or to the comorbid conditions that had been associated with MRSA infection is never clearly delineated. With the increasing prevalence of CA-MRSA, some of these uncertainties can now be clarified. Our study reveals interesting results. First, our findings verify that MRSA surpassed MSSA in both healthcare-associated and CA-associated bacteremia with comparable rate in each setting. The majority of CA-MRSA bacteremia is caused by SCCmec type IVa, but a substantial portion is also caused by SCCmec type II, traditionally associated with healthcare-associated infections. Likewise, SCCmec type II causes the majority of healthcare-associated infections, but a sizable portion is caused by SCCmec type IVa. It had been proposed that CA-MRSA strains eventually will be introduced into healthcare settings and nosocomial isolates will begin circulating in communities (6, 33, 38). The prevalence of SCCmec type IVa among intravenous narcotic users has been noted by others (34).

Second, we demonstrate that MRSA is associated with higher all cause mortality and persistent bacteremia, with a trend toward higher attributable mortality. After controlling for comorbid condition, illness severity, and the source, MRSA remains a strong predictor of mortality. These findings illustrate that MRSA-MSSA differences are authentic and reproducible. We now show that the MRSA-associated increased mortality is accounted for by SCCmec type II. Multivariate analysis, controlling for the source, comorbid conditions, illness severity, and treatment type, revealed that SCCmec type II is an independent predictor of all cause and attributable mortality. The association with higher mortality with SCCmec type II was also noted by others (6). These organisms had been reported to have lower antibiotic susceptibility compared to SCCmec type IV (34). Whether the higher mortality is due to differences in antibiotic susceptibility or virulence factors is unclear. We did not find SCCmec type-related differences in the vancomycin MIC, in the incidence of heteroresistance (defined by growth at 8 μg of vancomycin and tycoplanin/ml or with 12-μg/ml tycoplanin Etest strips), or in isolates with MICs of ≥2 μg (data not shown).

The association between SCCmec type IVa and metastatic infection was unexpected. This association was evident for all cases combined and after adjusting for the source of bacteremia. Although a small portion of IVC-related bacteremia was caused by SCCmec type IVa, the association with metastatic infection was evident. Furthermore, SCCmec type IVa-associated soft tissue infection, usually known for its favorable prognosis, was also associated with higher risk for metastatic infection. This subgroup analysis suggests that the relationship is genuine. The possible reasons for the SCCmec type-related difference in the rate of metastatic infection may be a varied expression of surface proteins that adhere to vascular endothelial cells and facilitate spread to other foci (29). Jacobsson et al. noted that community-associated infections were significantly more likely to be associated with metastatic foci, but these researchers did not perform SCCmec typing of their isolates (14). Fowler et al. reported an association between hematogenous complications and bacterial genotype in...
S. aureus infection and a predominance of SCCmec II in patients with hematogenous complications, but these authors did not stratify their cases according to the source (9). Additional studies are needed to verify SCCmec type–related differences and explain the discrepancy in hematogenous complications. This discrepancy might be due to region-related strain differences.

With respect to persistence, MRSA association with longer duration of bacteremia was independent of SCCmec type. It is probably related to the more potent effect of β-lactam antibiotics compared to other antibiotics used for MRSA. These findings suggest that SCCmec type may influence the pathogenesis and outcome of S. aureus bacteremia. Additional studies are needed to identify which virulence factors are the determinant of increased mortality with SCCmec type II and metastatic infection with SCCmec type IVa.

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