MAJOR ARTICLE

# Outcome of *Staphylococcus aureus* Bacteremia in Patients with Eradicable Foci versus Noneradicable Foci

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**To determine the outcome of *Staphylococcus aureus* bacteremia (SAB) on mortality, including the impact of methicillin resistance and an initial delay (≤48 h) of appropriate antibiotics, a retrospective cohort study including 238 patients with SAB was performed. By logistic regression, noneradicable or noneradicated foci, underlying cirrhosis, and cancer were found to be independent predictors of mortality. In patients with eradicable foci, there were no significant differences in the associated mortality rate between methicillin-resistant SAB (11%) and methicillin-susceptible SAB (13%), and between inappropriate (13%) and appropriate (10%) empirical therapy, respectively ($P = .79$ and $P = .78$, respectively). By logistic regression, it was found that, in the subgroup of patients with noneradicable foci, underlying cirrhosis (odds ratio [OR], 3.1) and methicillin-resistant SAB (OR, 2.4) were independently associated with mortality.**

*Staphylococcus aureus* is a major cause of hospital- and community-acquired infections, including bacteremia, endocarditis, pneumonia, septic arthritis, and wound infection. Despite several potent antistaphylococcal drugs, *S. aureus* bacteremia (SAB) is still a serious infection [1]. In recent years, some investigators have emphasized the importance of focus identification and eradication in the treatment of SAB [2, 3]. Furthermore, although the rate of the resistance to methicillin among *S. aureus* is increasing, the clinical impact of methicillin resistance remains controversial [4]. Besides this, because of the recent emergence of *S. aureus* resistant to vancomycin [5], the prudent use of vancomycin is essential. However, with some cases, methicillin-resistant *S. aureus* (MRSA) infections are not initially suspected because clues for *S. aureus* infection are lacking, and microbiological results, including antibiotic susceptibility data, are usually unavailable for ≥2 days. However, the relative effects of a delay in appropriate antibiotic treatment on the outcomes of patients with SAB are also unclear [4].

In this study, we evaluated the risk factors influencing the outcome of SAB. Furthermore, we compared the outcomes of SAB in patients with eradicable focus versus noneradicable focus and determined the impact of methicillin resistance on the outcome for patients with SAB and the effect of the inappropriate empirical antibiotic treatment on the outcome for patients with SAB.

## PATIENTS, MATERIALS, AND METHODS

***Study population.*** Seoul National University Hospital is a university-affiliated tertiary care hospital with 1500 beds. The hospital provides specialized medical and surgical care, including bone marrow transplantation for adult (>15 years of age) patients.

All patients with blood cultures positive for *S. aureus*

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were identified from a retrospective review of the computerized records of the Clinical Microbiology Laboratory for the period of 1 January 1998 through 31 October 2001. Only the first episode of SAB for each patient was included in the analysis. SAB without clinical significance and SAB with a mixture of organisms being cultivated from their blood samples were excluded.

***Microbiological tests.*** Identification of *S. aureus* was performed with Vitek GPI Cards. Antibiotic susceptibilities were determined using the disk diffusion method, following the recommendations of the NCCLS [6].

***Definitions.*** Bacteremia was defined as the presence of ⩾1 positive blood culture for *S. aureus.* It was considered clinically significant if *S. aureus* was isolated from ⩾1 blood culture and if the patients had signs and symptoms consistent with bacteremia [7]. No cases in which *S. aureus* was cultivated only in a peripheral intravenous line were included. SAB was considered to have been community acquired if *S. aureus* was isolated from cultures of blood samples obtained within 48 h after hospital admission, if the patient had not transferred from another hospital, and if the patient had any symptoms or signs suggestive of infection at admission [2]. Otherwise, SAB was considered to have been hospital acquired.

Previous antibiotic use was defined as treatment with antibiotics for >7 days during the month before the onset of SAB [7]. Previous surgery was defined as an operation within the month before the onset of SAB [7]. A history of MRSA colonization was defined as isolation of MRSA from any specimens (i.e., sputum, wound, and urine) within the 6 months before the onset of SAB. A hospital stay was defined as the length of hospital stay from the time of admission to the occurrence of SAB. Neutropenia was defined as an absolute neutrophil count of ⩽500 neutrophils/mm$^3$ when bacteremia occurred.

***Foci of bloodstream infection.*** The primary foci of infection were determined by use of the following definitions. Catheter-related infection was considered to be the source of bacteremia, modified from the previous study [8], if (1) the catheter had been in place for ⩾72 h; (2) the culture of a specimen of purulent drainage from the insertion site grew *S. aureus* that had the same resistance pattern as the culture strain from the peripheral blood, or the clinical signs improved after the catheter had been removed; and (3) no other source for bacteremia existed. We used such indirect clinical evidence of catheter-related infection in the absence of laboratory confirmation for catheter-related infection (i.e., quantitative culture of blood or semiquantitative culture of a catheter segment), which was not performed in our hospital during the study period. Pneumonia was considered to be the source of SAB if the patient had clinical symptoms and signs of a lower respiratory tract infection, and if there was radiological evidence of pulmonary infiltrates not attributable to other causes [8]. Soft-tissue infection was considered to be the source of SAB when patients had a pure culture of *S. aureus* from a tissue or a drainage specimen from the affected site and had signs of infection [8]. Surgical wound infection was defined according to the definitions of the Centers for Disease Control and Prevention [9]. Infective endocarditis was defined by the Duke criteria [10]. If a primary focus of infection could not be determined, it was considered to be unknown.

The primary foci of infections were divided into eradicable and noneradicable foci. Eradicable foci included surgically removable infections or drainable abscess and indwelling foreign bodies, such as peripheral and central intravenous catheters. Noneradicable foci included unknown primary site, pneumonia, endocarditis, and osteomyelitis or arthritis. Of the eradicable foci, eradicated foci included foci in which abscesses and indwelling foreign bodies had been drained or removed [2].

***Antibiotic treatment and outcome.*** Decisions regarding empirical antibiotic regimens were the responsibility of the primary care physician. The empirical antibiotic treatment was considered to be appropriate if the empirical therapy provided during the first 48 h after the onset of bacteremia included ⩾1 antibiotic to which the isolate was susceptible (for MRSA, always at least vancomycin or teicoplanin) and if the dose of the susceptible antibiotics was adequate. We used this arbitrary time interval (48 h) because the preliminary results from blood cultures were unavailable for at least this period.

The treatment outcome of SAB was measured as a SAB-related mortality and was defined as cases in which patients died within 8 weeks after the onset of SAB if there was no other explanation for death.

***Statistical analysis.*** The results were analyzed using the SPSS for Windows software package, version 10.0 (SPSS). The categorical variables were compared by Fisher's exact tests or Pearson $\chi^2$ tests, as appropriate, and the continuous variables were compared by Student's *t* test. All tests of significance were 2-tailed; $P \leqslant .05$ was considered to be significant. With the variables for which $P \leqslant .05$, the independent predictors of outcome of SAB as well as the risk factors for MRSA bacteremia were identified by means of stepwise conditional logistic regression analysis.

## RESULTS

***Clinical characteristics.*** Two hundred thirty-eight patients with clinically significant SAB were analyzed. Demographic data and clinical characteristics for these patients are shown in table 1. Of the 238 patients, 127 (53.4%) had MRSA bacteremia and 111 (46.6%) had methicillin-susceptible *S. aureus* (MSSA) bacteremia. The mean time to defervescence ($\pm$SD) was 5.3 $\pm$ 5.1 days (range, 1–26 days). Thirty-nine patients (16.4%) had metastatic infections. There were 186 hospital-acquired cases (78.2%) and 52 community-acquired cases (21.8%). Of the 52

**Table 1. Baseline clinical characteristics of patients with *Staphylococcus aureus* bacteremia.**

| Clinical characteristic | MRSA-infected patients ($n$ = 127) | MSSA-infected patients ($n$ = 111) | $P$ | Recipients of inappropriate empirical therapy ($n$ = 117) | Recipients of appropriate empirical therapy ($n$ = 121) | $P$ |
|---|---|---|---|---|---|---|
| Age, mean years ± SD | 56.7 ± 15.7 | 52.8 ± 16.4 | .07 | 54.2 ± 16.4 | 55.5 ± 15.9 | .56 |
| Male sex | 84 (66.1) | 72 (64.9) | .84 | 75 (64.1) | 81 (66.9) | .65 |
| Community-acquired infection[a] | 8 (6.3) | 44 (39.6) | <.001 | 11 (9.4) | 41 (33.9) | <.001 |
| Duration of hospital stay before onset of SAB, mean days ± SD | 33.9 ± 34.6 | 17.7 ± 34.3 | <.001 | 34.7 ± 38.9 | 18.3 ± 29.7 | <.001 |
| Primary site of infection | | | | | | |
| Unknown | 50 (39.4) | 43 (38.7) | .92 | 52 (44.4) | 41 (33.9) | .10 |
| Catheter-related infection | 31 (24.4) | 25 (22.5) | .73 | 30 (25.6) | 26 (21.5) | .45 |
| Pneumonia | 17 (13.4) | 18 (16.2) | .54 | 12 (10.3) | 23 (19.0) | .06 |
| Soft-tissue infection | 5 (3.9) | 14 (12.6) | .01 | 4 (3.4) | 15 (12.4) | .01 |
| Surgical wound infection | 16 (12.6) | 0 (0.0) | <.001 | 10 (8.5) | 6 (5.0) | .27 |
| Infective endocarditis | 1 (0.8) | 4 (3.6) | .19 | 2 (1.7) | 3 (2.5) | .68 |
| Osteomyelitis or arthritis | 2 (1.6) | 4 (3.6) | .42 | 1 (0.9) | 5 (4.1) | .21 |
| Other | 5 (3.9) | 3 (2.7) | .73 | 6 (5.1) | 2 (1.7) | .17 |
| Underlying disease or risk factor | | | | | | |
| Liver cirrhosis[a] | 17 (13.4) | 27 (24.3) | .03 | 19 (16.2) | 25 (20.7) | .38 |
| Cancer | 34 (26.8) | 25 (22.5) | .45 | 32 (27.4) | 27 (22.3) | .37 |
| Hematologic malignancy | 21 (16.5) | 26 (23.4) | .18 | 28 (23.9) | 19 (15.7) | .11 |
| End-stage renal disease | 27 (21.3) | 16 (14.4) | .17 | 25 (21.4) | 18 (14.9) | .19 |
| Infection acquired in the ICU[a] | 29 (22.8) | 1 (0.9) | <.001 | 19 (16.2) | 11 (9.1) | .10 |
| Previous antibiotic use[a] | 106 (83.5) | 37 (33.3) | <.001 | 88 (75.2) | 55 (45.5) | <.001 |
| Previous surgery[a] | 47 (37.0) | 6 (5.4) | <.001 | 35 (29.9) | 18 (14.9) | .005 |
| History of MRSA colonization | 32 (25.2) | 3 (2.7) | <.001 | 19 (16.2) | 16 (13.2) | .51 |
| Neutropenia | 17 (13.4) | 20 (18.0) | .33 | 23 (19.7) | 14 (11.6) | .09 |

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

[a] Independent risk factors for MRSA or MSSA bacteremia ($P \leq .05$ in a logistic regression model).

patients with community-acquired SAB, 8 (15.4%) had MRSA bacteremia, and all had predisposing risk factors for MRSA bacteremia. One hundred seventeen patients (49.2%) were treated with an inappropriate empirical antibiotic regimen. And 97 (76.4%) of 127 patients with MRSA bacteremia were treated with an inappropriate empirical antibiotic regimen; 20 (18.0%) of 111 patients with MSSA bacteremia were treated inappropriately.

***Predictors of mortality.*** The SAB-related mortality rate was 37.0% (88 of 238 patients), and 90% of the patients with fatal outcomes died within 28 days after the onset of bacteremia. Variables associated with mortality are shown in table 2. In a logistic regression analysis with the entire population ($n$ = 238), noneradicable foci or noneradicated foci and underlying diseases, such as cancer or liver cirrhosis, were independently associated with mortality (table 3).

***Mortality associated with methicillin resistance and inappropriate empirical antibiotic therapy in patients with eradicable foci.*** We divided primary sites of infections into 2 groups, such as eradicable foci and noneradicable foci, to determine the impact of methicillin resistance and inappropriate empirical antibiotic therapy on the outcomes of SAB (table 4). The difference in mortality between MRSA (6 [10.7%] of 56 patients) and MSSA (5 [12.5%] of 40 patients) bacteremia in patients with eradicable foci was not significant (OR, 0.84; 95% CI, 0.24–2.97; $P$ = .79). The difference in mortality between inappropriate empirical antibiotic therapy (6 [12.5%] of 48) and appropriate empirical antibiotic therapy (5 [10.4%] of 48) in patients with eradicable foci was not significant (OR, 1.23; 95% CI, 0.35–4.33; $P$ = .78).

***Mortality associated with methicillin resistance and inappropriate empirical antibiotic therapy in patients with noneradicable foci.*** MRSA bacteremia (45 [63.4%] of 71 patients died) in patients with noneradicable foci had worse outcome than did MSSA bacteremia (32 [45.1%] of 71 patients died; OR, 2.11; 95% CI, 1.08–4.13; $P$ = .03). And inappropriate empirical antibiotic therapy (44 [63.8%] of 69 patients died) in patients with noneradicable foci had worse outcome than did appropriate empirical antibiotic therapy (33 [45.2%] of 73 pa-

**Table 2. Variables associated with mortality in patients with *Staphylococcus aureus* bacteremia.**

| Variable | No. (%) of nonsurvivors | No. (%) of survivors | *P* |
|---|---|---|---|
| Primary foci of infections | | | |
| Noneradicable foci | 77 (54.2) | 65 (45.8) | <.001 |
| Eradicable foci | 11 (11.5) | 85 (88.5) | |
| Eradicated | 5 (6.8) | 69 (93.2) | .02 |
| Not eradicated | 6 (27.3) | 16 (72.7) | |
| Age | | | |
| ⩾65 years | 35 (46.1) | 41 (53.9) | .047 |
| <65 years | 53 (32.7) | 109 (67.3) | |
| Underlying disease | | | |
| Cancer | 33 (55.9) | 26 (44.1) | .001 |
| Liver cirrhosis | 26 (59.1) | 18 (40.9) | .001 |
| End-stage renal disease | 16 (37.2) | 27 (62.8) | .97 |
| Pathogen | | | |
| MRSA | 51 (40.2) | 76 (59.8) | .28 |
| MSSA | 37 (33.3) | 74 (66.7) | |
| Empirical antibiotic therapy received | | | |
| Inappropriate | 50 (42.7) | 67 (57.3) | .07 |
| Appropriate | 38 (31.4) | 83 (68.6) | |

**NOTE.** MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.*

tients died; OR, 2.13; 95% CI, 1.09–4.18; $P = .03$). A logistic regression analysis in the subgroup of patients with noneradicable foci ($n = 142$) revealed that underlying liver cirrhosis (OR, 3.08; 95% CI, 1.27–7.47) and methicillin resistance (OR, 2.40; 95% CI, 1.19–4.83) were independently associated with mortality.

## DISCUSSION

This study confirmed the importance of primary foci (i.e., eradicable foci vs. noneradicable foci) on the outcome of SAB. Several authors emphasized the importance of identifying and treating focus in the treatment of SAB. Iannini and Crossley [11] demonstrated that the prognosis of SAB with a removable focus of infection was good enough to justify the short-term therapy. Jensen et al. [2] and Jensen [3] showed that the mortality rate for patients with eradicable foci was significantly lower compared with that for patients with noneradicable foci. And our finding that patients with eradicated foci had better outcome than did those with noneradicated foci is also in line with findings of recent studies [2, 3].

There is controversy about whether methicillin resistance may adversely affect outcome. A recent meta-analysis [4] showed that MRSA bacteremia is associated with significantly higher mortality than is MSSA bacteremia. Our study did not find that the mortality for patients with MRSA bacteremia was significantly different from that for those with MSSA bacteremia. But subgroup analysis resulted in conflicting data; MRSA bacteremia in patients with noneradicable foci had worse outcome than did MSSA bacteremia, whereas the difference in mortality between MRSA and MSSA bacteremia in patients with eradicable foci was not significant. The reason for this difference relating to the primary foci is unclear. One explanation is that vancomycin treatment might be less effective than antistaphylococcal $\beta$-lactam treatment for MSSA infection in serious infections, such as those with noneradicable foci. It is well known that glycopeptides are intrinsically less active against staphylococci than are antistaphylococcal $\beta$-lactams [12]. Suboptimal clinical results have been demonstrated for vanco-

**Table 3. Results of the logistic regression analysis to identify independent predictors of mortality among patients with *Staphylococcus aureus* bacteremia.**

| Predictor of mortality | Adjusted OR (95% CI) | *P* |
|---|---|---|
| Noneradicated foci[a] | 4.17 (1.09–3.62) | .04 |
| Noneradicable foci | 3.75 (1.33–10.55) | .01 |
| Liver cirrhosis | 2.25 (1.04–4.84) | .04 |
| Cancer | 2.11 (1.06–4.20) | .03 |
| Old age[b] | 1.88 (0.97–3.62) | .06 |

[a] The variable "noneradicated foci" comprises noneradicable foci and eradicable foci not actually eradicated.
[b] Age, ⩾65 years.

**Table 4. Mortality associated with methicillin resistance and inappropriate empirical antibiotic therapy related to eradicable and noneradicable foci of *Staphylococcus aureus* bacteremia.**

| Foci, variable | No. (%) of nonsurvivors | No. (%) of survivors | *P* |
|---|---|---|---|
| Eradicable foci | | | |
| Pathogen | | | |
| MRSA | 6 (10.7) | 50 (89.3) | .79 |
| MSSA | 5 (12.5) | 35 (87.5) | |
| Empirical antibiotic therapy | | | |
| Inappropriate | 6 (12.5) | 42 (87.5) | .78 |
| Appropriate | 5 (10.4) | 43 (89.6) | |
| Noneradicable foci | | | |
| Pathogen | | | |
| MRSA | 45 (63.4) | 26 (36.6) | .03 |
| MSSA | 32 (45.1) | 39 (54.9) | |
| Empirical antibiotic therapy | | | |
| Inappropriate | 44 (63.8) | 25 (36.2) | .03 |
| Appropriate | 33 (45.2) | 40 (54.8) | |

**NOTE.** MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

mycin treatment in other serious MRSA infections, such as MRSA endocarditis [13] and *S. aureus* bacteremic pneumonia [14]. A recent well-designed case-control study [15] also demonstrated that MRSA bacteremia had a higher attributable mortality rate than did MSSA bacteremia among critically ill patients. Another explanation is that the patients with eradicable foci of infections might be more easily treated, and the magnitude of effect of MRSA on mortality was lower in the patients with eradicable foci. A recent meta-analysis [4] showed that studies in which $\geq$40% of patients had catheter-related SAB had a lower pooled OR (1.57) than did studies in which <40% of patients had catheter-related SAB (OR, 1.87).

There are conflicting data regarding the outcome of the inappropriate empirical antibiotic therapy for SAB. Conterno et al. [16] reported that an inappropriate empirical antibiotic treatment adversely affected mortality (24 [57%] of 42, for inappropriate empirical antibiotic treatment, vs. 22 [30%] of 74, for appropriate empirical antibiotic treatment; $P < .01$). Soriano et al. [7] also reported that inappropriate empirical antibiotic therapy adversely affected the mortality (OR, 2.13; 95% CI, 1.21–3.75). In contrast, Roghmann [17] reported the relative risk of death due to an inappropriate empirical antibiotic therapy was <1 (relative risk, 0.82; 95% CI, 0.36–1.88). Our study did not show a significant association between the initial delay in appropriate antibiotic treatment for the first 48 h and the outcome of SAB, especially in patients with eradicable foci, although the 95% CI was relatively wide (OR, 1.23; 95% CI, 0.35–4.33). Therefore, we can infer the important idea from our results. When SAB might be suspected, the most significant prognostic variables would be the primary site of infection (i.e., eradicable or eradicated) and underlying disease (i.e., cancer or liver cirrhosis). And if the primary site of infection is easily eradicable, glycopeptide might be restricted until preliminary microbiologic reports are available. However, subgroup analysis showed that the inappropriate empirical antibiotic therapy in patients with noneradicable foci adversely affected the outcome (OR, 2.13; 95% CI, 1.09–4.18). If this finding were true, delayed treatment might be one of the reasons why MRSA bacteremia in patients with noneradicable foci may cause worse outcomes than MSSA bacteremia. But the receipt of an inappropriate empirical antibiotic therapy was highly correlated with having MRSA as opposed to MSSA. A logistic regression analysis of the subgroup of patients with noneradicable foci did not reveal that an inappropriate empirical antibiotic therapy was associated with mortality (adjusted OR, 1.56; 95% CI, 0.69–3.49). A randomized clinical trial can definitely answer whether an inappropriate empirical antibiotic therapy may adversely affect the outcome in the treatment of SAB, although this clinical trial would be difficult to perform in view of ethical concerns.

In this study, the overall mortality rate for patients with SAB was relatively high (37%; 88 of 238 patients), whereas other studies have reported mortality rates of 16%–43% [16]. This is because our study included patients with rapidly fatal cases (i.e., patients who died before initial microbiological reports were received). Many of our patients had other serious underlying conditions, including old age, liver cirrhosis, and cancer. This may limit the generalizability of our findings. It is noteworthy that 44 (18%) of our 238 patients had liver cirrhosis, reflecting the high prevalence (8%) of chronic hepatitis B virus infection among the general population in Korea [18]. Our study did not determine the factors influencing the attending physician's delay in administering an appropriate antibiotic treatment; therefore, we can not exclude unmeasured confounding factors.

In conclusion, our data demonstrated that the primary site of infection and underlying diseases were the independent predictors of mortality associated with SAB. Furthermore, our findings suggest that the mortality due to MRSA and MSSA bacteremia might be similar in patients with eradicable foci, but MRSA bacteremia in patients with noneradicable foci had a worse outcome than did MSSA. Our findings support the notion that an initial delay in the use of appropriate antibiotics for the first 2 days might not adversely affect the outcome of SAB, especially in eradicable foci.

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