Predictive Factors for Metastatic Infection in Patients With Bacteremia Caused by Methicillin-Sensitive Staphylococcus aureus

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Abstract: Background: Metastatic infections such as infective endocarditis and psoas abscess are serious complications of Staphylococcus aureus bacteremia because failure to identify these infections may result in bacteremia relapse or poor prognosis. In the present study, we determined the predictive factors for metastatic infection due to methicillin-sensitive S. aureus bacteremia. Methods: A retrospective cohort study was conducted among patients with methicillin-sensitive S. aureus bacteremia at the Jikei University Hospital between January 2008 and December 2012. Factors analyzed included the underlying disease, initial antimicrobial treatment and primary site of infection. Results: During the 5-year study period, 73 patients met the inclusion criteria and were assessed. The most common primary site of bacteremia was catheter-related bloodstream infection (25/73 [34.2%]). Metastatic infection occurred in 14 of 73 patients (19.2%) (infective endocarditis [3], septic pulmonary abscess [3], spondylitis [4], psoas abscess [4], epidural abscess [3] and septic arthritis [1]). Six patients had multiple metastatic infections. Multivariate analysis revealed that the predictive factors associated with the development of metastatic infection were a delay in appropriate antimicrobial treatment of >48 hours, persistent fever for >72 hours after starting antibiotic treatment and lowest C-reactive protein levels of >3 mg/dL during 2 weeks after the onset of bacteremia. Conclusions: This study demonstrated that additional diagnostic tests should be conducted to identify metastatic infection, particularly in patients with delayed antimicrobial treatment, persistent fever and persistently high C-reactive protein levels.


Staphylococcus aureus is an important pathogen of bloodstream infection, particularly healthcare-associated and nosocomial bloodstream infections. 1,2 Metastatic infection is a serious complication of both methicillin-sensitive S. aureus (MSSA) and methicillin-resistant S. aureus bacteremia because failure in its identification may result in bacteremia relapse. Long-term antibiotic treatment is needed for patients with metastatic infections due to S. aureus bacteremia. Hence, metastatic infections should be detected before antibiotic administration is completed. Previous studies have shown that the incidence of metastatic infection due to S. aureus bacteremia ranges between 13% and 39%. 3–10 In addition, the predictive factors for metastatic infection due to S. aureus bacteremia include community acquisition, 11 delay in adequate treatment, 12 persistent positive blood culture results 9,11 and persistent fever.11

C-reactive protein (CRP) is a frequently used biomarker in clinical practice and various studies have evaluated its utility in bacterial infections. However, few studies have investigated the role of CRP levels during MSSA bacteremia. 9,12 The present study aimed to determine the predictive factors and evaluate the role of CRP levels in metastatic infection due to MSSA bacteremia.

SUBJECTS AND METHODS

Study Population

The study was conducted at the Jikei University Hospital, which is a 1,075-bed hospital in Tokyo, Japan. This study included patients aged 20 years or older whose blood culture tested positive for MSSA between January 2008 and December 2012.

Exclusion Criteria

To determine the predictive factors for metastatic infection due to MSSA bacteremia, patients were excluded from this study according to the following criteria: polymicrobial bacteremia, death or transfer to another hospital within 3 months after the initial positive blood culture result was obtained.

Study Design

A retrospective cohort study was conducted to evaluate the predictive factors for metastatic infection due to MSSA bacteremia. We assessed the following characteristics for each patient from medical records: age, sex, presence of an underlying disease, shock status, community acquisition, use of immunosuppressive agents, neutropenia, CRP levels at the time of collection of blood samples and after treatment, delay in antibiotic therapy, persistent fever and primary site of infection.

Definitions

MSSA bacteremia was defined as the identification of MSSA in blood culture and a clinical course consistent with S. aureus infection. Metastatic infection was defined as deep-seated infection, including endocarditis and muscle abscess, detected within 3 months after the initial positive blood culture result was obtained. Community acquisition was defined as a positive blood culture result and clinical evidence of infection that developed within 48 hours after hospital admission if the patient did not come in contact with any other hospital or clinic.
Microbiological Methods

Blood cultures, each consisting of aerobic and anaerobic samples, were processed at the clinical laboratory of our university-affiliated hospital. MSSA identification and antibiotic susceptibility tests were performed on a MicroScan WalkAway 96 system (Dade Behring, Inc, West Sacramento, CA). The Clinical Laboratory and Standards Institute criteria were used to define susceptibility or resistance to the antimicrobial agents.

Statistical Analyses

The \( \chi^2 \) test or Fisher's exact test was used to compare categorical variables; Student's \( t \) test and Mann-Whitney's \( U \) test were used to compare continuous variables, as needed. To determine the independent predictive factors for metastatic infections, a multiple logistic regression model was used to control the effects of confounding variables. Factors that showed significant difference between the present and absent groups were included in the multiple logistic regression model. The results of logistic regression analysis were reported as adjusted odds ratio (AOR) with 95% confidence interval (CI). All \( P \)-values were 2-tailed, and statistical significance was set at \( P < 0.05 \). All statistical analyses were performed using IBM SPSS Statistics 19 (IBM Japan, Ltd, Tokyo, Japan).

RESULTS

Clinical Characteristics of Patients With MSSA Bacteremia and the Site of Metastatic Infection

One or more cultures of blood specimens from 117 patients were positive for MSSA during the 5-year study period. Forty-four patients were excluded from the study because of polymicrobial bacteremia, death or transfer to another hospital within 3 months after the initial positive blood culture result was obtained. Finally, 73 patients were included in this study. Of these, 67.1% (49/73) were men, and the median age of all patients was 67 years. Fifty patients (68.5%) had an underlying disease (31.5%, 23/73), followed by chronic kidney disease (24.7%, 18/73). Fourteen patients (19.2%) were infected with MSSA as a community-acquired infection. Hematological data at the time of blood culture sampling showed that 5 of 73 patients (6.8%) had neutropenia (<500 cells/mm\(^3\)). Metastatic infection occurred in 14 of 73 patients (19.2%) as follows: muscle abscess (5, including 4 with psoas abscesses), infective endocarditis (3), septic pulmonary abscess (3), epidural abscess (4), psoas abscess (2), muscle abscess and septic pulmonary abscess (1), epidural abscess and spondylodiscitis (1), septic pulmonary abscess and spondylodiscitis (1) and multiple muscle abscesses (1).

Clinical Features of Patients and Predictive Factors for Metastatic Infections

We demonstrated the relationship between the clinical features of patients and metastatic infection (Table 2). Univariate analysis revealed that there was no significant difference in the clinical background between patients with and without metastatic infection due to MSSA bacteremia. Furthermore, neutropenia was not associated with metastatic infections. In

### Table 1. Localization of metastatic infections

<table>
<thead>
<tr>
<th>Localization</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>73</td>
</tr>
<tr>
<td>Absent</td>
<td>59 (80.8%)</td>
</tr>
<tr>
<td>Present</td>
<td>14 (19.2%)</td>
</tr>
<tr>
<td>Muscle abscess</td>
<td>5</td>
</tr>
<tr>
<td>Psoas abscess</td>
<td>4</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
</tr>
<tr>
<td>Spondylodiscitis</td>
<td>4</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>3</td>
</tr>
<tr>
<td>Joint</td>
<td>1</td>
</tr>
<tr>
<td>Total number of metastatic infections</td>
<td>20</td>
</tr>
</tbody>
</table>

### Table 2. Clinical characteristics of patients with MSSA bacteremia

<table>
<thead>
<tr>
<th>Metastatic infection</th>
<th>Present (n = 14)</th>
<th>Absent (n = 59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), yr</td>
<td>69 (37–80)</td>
<td>64 (31–95)</td>
<td>0.877</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>9 (64.3)</td>
<td>40 (67.8)</td>
<td>0.533</td>
</tr>
<tr>
<td>Underlying disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>0 (0)</td>
<td>3 (5.1)</td>
<td>0.523</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>0 (0)</td>
<td>4 (6.8)</td>
<td>0.418</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>2 (14.3)</td>
<td>11 (18.6)</td>
<td>0.524</td>
</tr>
<tr>
<td>Diabetic mellitus</td>
<td>2 (14.3)</td>
<td>21 (35.6)</td>
<td>0.108</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (14.3)</td>
<td>16 (27.1)</td>
<td>0.264</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1 (7.1)</td>
<td>4 (6.8)</td>
<td>0.667</td>
</tr>
<tr>
<td>Shock (systolic blood pressure &lt; 90 mm Hg)</td>
<td>0 (0)</td>
<td>3 (5.1)</td>
<td>0.523</td>
</tr>
<tr>
<td>Community acquisition, n (%)</td>
<td>5 (35.7)</td>
<td>9 (15.3)</td>
<td>0.090</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>3 (21.4)</td>
<td>9 (15.3)</td>
<td>0.415</td>
</tr>
<tr>
<td>Immunosuppressive agent</td>
<td>3 (21.4)</td>
<td>13 (22.0)</td>
<td>0.636</td>
</tr>
</tbody>
</table>

Hematological laboratory data at onset of bacteremia

| Neutropenia (<500/mL), n (%) | 0 (0) | 5 (8.5) | 0.333 |
| CRP > 10 mg/dL | 10 (71.4) | 16 (27.1) | 0.003 |

CRP, C-reactive protein; MSSA, methicillin-sensitive *Staphylococcus aureus*. 
contrast, CRP levels of >10 mg/dL at the onset of MSSA bacteremia were a predictive factor for metastatic infections.

**Relationship Between Primary Site of Bacteremia and Metastatic Infections**

The source of infection was identified in 52 of 73 patients (71.2%) (Table 3). The most common primary site of infection was catheter-associated bloodstream infection (34.2%, 25/73), followed by skin and soft tissue infection (20.5%, 15/73). Univariate analysis indicated that the rate of metastatic infection due to MSSA bacteremia was significantly lower in the patients with central venous catheter-associated bloodstream infection.

**Antibiotic Treatment and Outcome**

Appropriate antimicrobial treatment was administered to 62 patients within 48 hours after their blood culture was obtained. Delay in the administration of appropriate antimicrobial treatment was significantly higher among patients with metastatic infection than in those without metastatic infection (7/14 patients, 50.0% versus 4/59 patients, 6.8%; P = 0.0004) (Table 4). In addition, persistent fever for >72 hours after starting antibiotic treatment was associated with an increased incidence of metastatic infection. Lowest CRP levels of >3 mg/dL during 2 weeks after the onset of bacteremia were a predictive factor for metastatic infections.

Among 23 patients who provided blood cultures >48 hours after antibiotic treatment, persistent positive blood cultures were more frequent in those with metastatic infections (60.0%, 3/5) than in those without metastatic infections (11.1%, 2/18).

**Analyses of Predictive Factors in Logistic Regression Analysis**

The results of univariate analysis revealed that CRP levels of >10 mg/dL when blood culture was obtained, treatment delay of >48 hours, persistent fever for >72 hours and lowest CRP levels of >3 mg/dL during 2 weeks after the onset of bacteremia were significantly associated with metastatic infection. In addition to these variables, diabetes mellitus, community acquisition and an unknown primary site of MSSA bacteremia were subjected to multivariate analysis. Multivariate analysis using the logistic regression model identified the following independent predictive factors for metastatic infection: treatment delay (AOR = 14.041; 95% CI = 1.934–101.926; P = 0.009), persistent fever for >72 hours (AOR = 15.631; 95% CI = 2.113–115.618; P = 0.007) and lowest CRP levels of >3 mg/dL after antibiotic treatment (AOR = 17.95; 95% CI = 2.736–177.733; P = 0.003) (Table 5).

**DISCUSSION**

Although various examinations, including echocardiography for endocarditis, computed tomography for septic pulmonary embolism, magnetic resonance imaging for spondylitis and 18F-fluorodeoxyglucose-positron emission tomography in combination with low-dose computed tomography are required to identify metastatic infections, it is difficult to diagnose uncomplicated *S. aureus* bacteremia. Fowler et al defined uncomplicated *S. aureus* bacteremia as that in patients with no symptoms or signs of infection within a 12-week follow-up period. Similarly, in this study, we defined uncomplicated *S. aureus* bacteremia as that in patients who did not develop metastatic infection within 3 months after the initial positive blood culture result.

In this study, 14 of 73 patients (19.2%) had metastatic infection due to MSSA bacteremia, which is similar to the results reported previously.

<table>
<thead>
<tr>
<th>TABLE 3. The primary site of MSSA bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic infection</strong></td>
</tr>
<tr>
<td>Present (n = 14), n (%)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Primary site of infection</td>
</tr>
<tr>
<td>Intravascular catheter</td>
</tr>
<tr>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
</tr>
<tr>
<td>Respiratory tract</td>
</tr>
<tr>
<td>Urinary tract</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
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**TABLE 4. Antibiotic treatment and outcome**

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<td>Present (n = 14)</td>
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</tr>
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<td>CRP &gt; 3.0 mg/dL</td>
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**TABLE 5. Predictive factors of the metastatic infection due to MSSA bacteremia in the logistic regression analysis**

<table>
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<th>AOR</th>
<th>95% CI</th>
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CRP, C-reactive protein; CI, confidence interval; CRP, C-reactive protein; MSSA, methicillin-sensitive *Staphylococcus aureus*.

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<td>CRP &gt; 3.0 mg/dL</td>
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AOR, adjusted odds ratio; CI, confidence interval; CRP, C-reactive protein; MSSA, methicillin-sensitive *Staphylococcus aureus*. 

Horino et al
the present study demonstrated that a delay in appropriate anti-
biotic treatment was a risk factor for metastatic infection due to
MSSA bacteremia. These results suggest that a delay in appro-
priate antibiotic treatment leads to poor prognosis and severe
complications during *S. aureus* bacteremia.

Guidelines on the diagnosis and management of pro-
sthetic joint infections have stated that combination of an
abnormal sedimentation rate and CRP levels seems to provide
the best combination of sensitivity and specificity.13 Tshaikowsky et al19 showed that presence of high CRP levels
was not a predictive factor for mortality due to bacteremia,
whereas other studies indicated that CRP levels in nonsurvivor
patients were significantly higher than those in survivor pa-

tients.17,18 Moreover, Lesens et al9 demonstrated that sustained
bacteremia was significantly associated with metastatic infec-
tion and higher frequency of CRP levels of $>$100 mg/L. Con-
versely, Vos et al20 demonstrated that CRP levels on admission
were not significantly different in patients with and without
metastatic infection. Similarly, in the present study, CRP levels
of $>$10 mg/dL at the onset of MSSA bacteremia were not
significantly associated with metastatic infections in logistic
regression analysis, although we observed that this was a pre-
dictive factor for metastatic infections in univariate analysis.

Because a minimum of 2 weeks of antimicrobial treat-
ment is recommended for adults with uncomplicated
bacteremia, clinicians at our institution determine whether
antimicrobial treatment should be continued or not within
approximately 2 weeks after starting antibiotic administra-
tion.19 Therefore, we investigated the lowest CRP levels dur-
ing 2 weeks after the onset of MSSA bacteremia and
demonstrated that lowest CRP levels of $>$3 mg/dL were signif-
ically associated with metastatic infection. Welsch et al21 dem-
onstrated that CRP levels in patients with complications were
persistently high after pancreatic resections. These results sug-
gested that persistently high CRP levels were associated with
complications because CRP levels increase after tissue injury.22
Thus, persistently high CRP levels may have an important role
compared with CRP levels at the diagnosis of MSSA bacteri-
aemia. Therefore, we should aggressively examine for metastatic
infections in patients with unexplained persistently high CRP
levels even after adequate antibiotic treatment.

The most important limitation of this study is that it was
retrospective. CRP levels were not measured serially during the
2-week study. In addition, 5 of 23 patients who provided blood
cultures $>$48 hours after antibiotic treatment had positive
results; other studies have indicated that persistent positive blood
cultures are significantly associated with metastatic infec-
tions.9,11,12 Therefore, we could not confirm whether persistent
positive blood cultures were a predictive factor because blood
cultures were not obtained 48 hours after antibiotic treatment
in all patients. Moreover, in this study, routine transthoracic ech-
cardiography was performed in 28 of 73 patients (38.4%), and
transesophageal echocardiography was performed in only 1
patient. However, 1 patient with metastatic infection did not
have persistent positive blood cultures 48 hours after appropri-
ate antibiotic treatment, and vegetation was not detected with
transthoracic echocardiography. Thus, we could not estimate
the presence of metastatic infections only on the basis of the
results obtained from blood cultures and echocardiography.

In conclusion, metastatic infections may be present
in patients with MSSA bacteremia, although they do not have any
localized symptom or persistent positive bacteremia. Therefore,
we should observe the predictive factors for metastatic
infections, including persistent fever, treatment delay and
persistently high CRP levels.

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