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.

Key Indexing Terms: *Staphylococcus aureus*; Bacteremia; Metastatic infection; Predictive factors. **[Am J Med Sci 2015;349(1):24–28.]**

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.

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Accordingly, 13 patients did not meet the criteria for community acquisition because of healthcare-associated infections: patients who visited an outpatient clinic (7), patients receiving hemodialysis (4) and patients with a central venous catheter (2). The source of MSSA bacteremia was determined by comparison with other MSSA-positive cultures or a clinical description by the physician in the medical records. Appropriate antimicrobial treatment was defined as use of antibiotics proven to be effective *in vitro* against MSSA isolated from blood culture. Neutropenia was defined as an absolute neutrophil count of <500 cells per cubic millimeter. Patients without any metastatic infection were defined as those having bacteremia without any complications such as abscess, spondylitis or relapse of bacteremia for 3 months after the initial positive blood culture result. A delay in antibiotic therapy was defined as not receiving appropriate antimicrobial treatment within 48 hours of a positive blood culture result.

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 χ^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, with diabetes mellitus being the most common (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 abscess), infective endocarditis (3), septic pulmonary abscess (3), spondylodiscitis (4), epidural abscess (3) and septic arthritis (1). Six patients had multiple metastatic infections (Table 1), such as muscle abscess and epidural 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).

TABLE 1. Localization of metastatic infections

Localization	Number of patients
Total number of patients	73
Absent	59 (80.8%)
Present	14 (19.2%)
Muscle abscess	5
Psoas abscess	4
Endocarditis	3
Lung	3
Spondylodiscitis	4
Epidural abscess	3
Joint	1
Total number of metastatic infections	20

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 2. Clinical characteristics of patients with MSSA bacteremia

	Metastatic infection		
	Present (n = 14)	Absent (n = 59)	*P*
Age, median (range), yr	69 (37–80)	64 (31–95)	0.877
Male gender, n (%)	9 (64.3)	40 (67.8)	0.533
Underlying disease, n (%)			
Leukemia	0 (0)	3 (5.1)	0.523
Malignant lymphoma	0 (0)	4 (6.8)	0.418
Solid tumor	2 (14.3)	11 (18.6)	0.524
Diabetic mellitus	2 (14.3)	21 (35.6)	0.108
Chronic kidney disease	2 (14.3)	16 (27.1)	0.264
Liver cirrhosis	1 (7.1)	4 (6.8)	0.667
Shock (systolic blood pressure < 90 mm Hg)	0 (0)	3 (5.1)	0.523
Community acquisition, n (%)	5 (35.7)	9 (15.3)	0.090
Medication, n (%)			
Steroid	3 (21.4)	9 (15.3)	0.415
Immunosuppressive agent	3 (21.4)	13 (22.0)	0.636
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 = 2.736–117.733; $P = 0.003$) (Table 5).

TABLE 3. The primary site of MSSA bacteremia

	Metastatic infection		
	Present (n = 14), n (%)	Absent (n = 59), n (%)	*P*
Primary site of infection			
Intravascular catheter	1 (7.1)	24 (40.7)	0.140
Central venous catheter	0 (0)	21 (35.6)	0.005
Skin and soft tissue infection	3 (21.4)	12 (20.3)	0.591
Respiratory tract	0 (0)	4 (6.8)	0.418
Urinary tract	3 (21.4)	5 (8.5)	0.175
Unknown	7 (50.0)	14 (23.7)	0.056

MSSA, methicillin-sensitive *Staphylococcus aureus*.

TABLE 4. Antibiotic treatment and outcome

	Metastatic infection		
	Present (n = 14)	Absent (n = 59)	*P*
Treatment delay >48 hours, n (%)	7 (50.0)	4 (6.8)	0.0004
Persistent fever >72 hours, n (%)	6 (42.9)	5 (8.5)	0.0047
CRP > 3.0 mg/dL	9 (64.3)	19 (32.2)	0.0002

CRP, C-reactive protein.

DISCUSSION

Although various examinations, including echocardiography for endocarditis, computed tomography for septic pulmonary embolism, magnetic resonance imaging for spondylitis and 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.[5,11] 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.[3–8,10] In the study by Cuijpers et al,[4] 26% of patients with metastatic infection due to *S. aureus* bacteremia did not have localizing signs and symptoms of metastatic infection. Similarly, in the present study, 33.3% of patients with metastatic infection did not have localizing signs and symptoms of metastatic infection. Thus, we should pay attention to the predictive factors for metastatic infections other than signs or symptoms.

The time of administration of appropriate antibiotics is a very important factor affecting the prognosis of *S. aureus* bacteremia.[12] Paul et al[13] demonstrated that compared with patients receiving appropriate treatment during methicillin-resistant *S. aureus* bacteremia, the mortality rate in patients not receiving appropriate antibiotic treatment within 48 hours of a positive blood culture result was significantly high. Similarly, Bassetti et al[14] showed that the administration of inappropriate antibiotics was significantly associated with high mortality in patients with *S. aureus* bacteremia. In addition,

TABLE 5. Predictive factors of the metastatic infection due to MSSA bacteremia in the logistic regression analysis

	AOR	95% CI	*P*
Treatment delay >48 hours, n (%)	14.041	1.934–101.926	0.009
Persistent fever >72 hours, n (%)	15.631	2.113–115.618	0.007
CRP > 3.0 mg/dL	17.95	2.736–117.733	0.003

AOR, adjusted odds ratio; CI, confidence interval; CRP, C-reactive protein; MSSA, methicillin-sensitive *Staphylococcus aureus*.

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

Guidelines on the diagnosis and management of prosthetic joint infections have stated that combination of an abnormal sedimentation rate and CRP levels seems to provide the best combination of sensitivity and specificity.[15] Tschaikowsky et al[16] 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 patients.[17,18] Moreover, Lesens et al[9] demonstrated that sustained bacteremia was significantly associated with metastatic infection and higher frequency of CRP levels of >100 mg/L. Conversely, Vos et al[12] 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 predictive factor for metastatic infections in univariate analysis.

Because a minimum of 2 weeks of antimicrobial treatment 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 administration.[19,20] Therefore, we investigated the lowest CRP levels during 2 weeks after the onset of MSSA bacteremia and demonstrated that lowest CRP levels of >3 mg/dL were significantly associated with metastatic infection. Welsch et al[21] demonstrated that CRP levels in patients with complications were persistently high after pancreatic resections. These results suggested 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 bacteremia. 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 infections.[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 echocardiography 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 appropriate 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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