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*.