

Clinical Differences between Methicillin-Resistant and -Susceptible *Staphylococcus aureus* Bacteremia in Adult Patients at a Tertiary Hospital in Japan

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Abstract

To determine clinical differences in features of methicillin-susceptible and resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) bacteremia, 15 adult patients with MRSA bacteremia were compared with 30 adult patients with MSSA bacteremia who were hospitalized during 2015 – 2018.

Compared with MSSA bacteremia patients, MRSA bacteremia patients had a higher age (mean age, 82.0 years and 72.5 years, respectively) and were more likely to have diabetes mellitus significantly ($p=0.04$). Liver and kidney functions were also significantly decreased in MRSA bacteremia patients compared with MSSA bacteremia patients ($p=0.037$, $p=0.001$ and $p=0.015$, respectively). Moreover, MRSA bacteremia patients showed a much higher mortality rate than MSSA bacteremia patients (60% and 20%, respectively; odds ratio: 2.66, 95% CI: 1.806-4.288, $p=0.007$).

These data suggest that MRSA bacteremia is more lethal than MSSA bacteremia in adults. Thus, caution should be taken when *Staphylococcus aureus* is isolated from the blood of patients who are elderly, diabetic, or have liver and kidney dysfunction because MRSA can be more possible pathogens rather than MSSA.

Keywords: Age; Methicillin-resistant *Staphylococcus aureus* (MRSA); Methicillin-susceptible *Staphylococcus aureus* (MSSA); Liver dysfunction; Kidney dysfunction

Introduction

Staphylococcus aureus is a common pathogen that is susceptible to antibiotics usually, including penicillins. However, methicillin-resistant *Staphylococcus aureus* (MRSA) has recently become representative for community- and hospital-acquired infections, and a multinational surveillance study suggested a high prevalence of MRSA in many countries [1,2]. Various MRSA clones have been suggested to spread among the community and/or hospitals, as well as among countries. In Japan, MRSA bacteremia is a serious issue, which occurs frequently, exhibits resistance to antibiotics, and is related with high mortality [3].

Up to 20% of all individuals with bacteremia in United States hospitals and approximately 31% of those in intensive care units of Spanish hospitals have MRSA bacteremia [4,5]. Even with appropriate antibiotic therapy, reported mortality and morbidity rates related with MRSA bacteremia are higher than those for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia, and reported mortality rate of MRSA bacteremia ranges 30% –40% [6-9].

In this investigation, we studied and compared clinical features of MRSA and MSSA bacteremia in adult patients.

Materials and Methods

Diagnostic and Patients

This study enrolled 45 adult patients (20 years or older) with *Staphylococcus aureus* bacteremia who were admitted to Tohoku Medical and Pharmaceutical University between November 2015 and December 2018. Bacteremia was defined as follows: one or more positive blood cultures from patients with clinical signs of infection, e.g., chills, fever, and sweats with or without local signs and symptoms. Age, male/female, underlying disease, clinical features, and laboratory data were evaluated. If MRSA had been isolated from the same patient on several occasions within the 3-year period, only the first episode of MRSA bacteremia was reviewed. This study was approved by the Committee for Clinical Scientific Research of Tohoku Medical and Pharmaceutical University Hospital in Oct 09, 2015 as No. ID2015-2-011 and the patients whose specimens were used provided written informed consent.

Identification of bacteria

Blood samples were cultured in BacT/Alert bottles (SysmexbioMérieux, Kobe, Japan). Rapid identification of the pathogens and antimicrobial susceptibility test of positive samples were performed using the MicroScanWalkAway 96-plus system (Siemens, Munich, Germany). All *Staphylococcus aureus* isolates were identified by Gram staining, colony morphological analysis, and catalase and

coagulase tests. Isolates were identified as MRSA if the minimum inhibitory concentration (MIC) of oxacillin was $\pm 4 \mu\text{g/mL}$.

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Data collection and statistical analysis

Clinical and demographic data that were normally distributed were subjected to analysis of variance, with Fisher's exact test for multiple comparisons. In addition, those that were non-normally distributed were analyzed by non-parametric statistics, such as the Mann-Whitney U-rank test. The results were corrected using the Bonferroni method when further analysis was necessary. Spearman's rank correlation was performed to examine relationships among various parameters. Survival of MRSA and MSSA bacteremia patients was analyzed by Kaplan-Meier curves. All data are expressed as mean \pm SD. p-values <0.05 denoted statistical significance. All analyses were carried out using Statview software (Abacus Concepts, Cary, NC, USA).

Results

Patients and complications

At first, we examined demographic and baseline characteristics of adults with MRSA (n=15) and MSSA (n=30) bacteremia (Table 1). In both groups, the majority of patients who were admitted and required critical care were elderly, as shown by the high mean age. We did not found significant differences in sex or most underlying diseases between the MRSA and MSSA groups. However, MRSA bacteremia patients were significantly more likely to have diabetes mellitus than MSSA bacteremia patients (p=0.04).

	MRSA (n = 15)	MSSA (n = 30)	p-value
Age(y.o.)	82.0 \pm 8.4	72.5 \pm 18.5	p=0.008**
Male/Female			
Male	12 (80.0%)	21 (70.0%)	p=0.47
Female	3 (20.0%)	9 (30.0%)	
Wards			
Respiratory	1 (6.7%)	2 (6.7%)	p=0.52
Cardiology	6 (40.0%)	5 (16.7%)	p=0.08
Gastrointestine	1 (6.7%)	7 (23.3%)	p=0.08
Surgery	0	2 (6.7%)	p=0.30
Neurology	0	4 (13.3%)	p=0.13
Collagen diseases	1 (6.7%)	1 (3.3%)	p=0.60
Orthopedics	0	2 (6.7%)	p=0.30
Diabetes mellitus	2 (13.3%)	0	p=0.04*

General medicine	2 (13.3%)	2 (6.7%)	p=0.52
Nephrology	0	1 (3.3%)	p=0.47
Rehabilitation	0	1 (3.3%)	p=0.47
Emergency medicine	2 (13.3%)	3 (10.0%)	p=0.73

Table 1: Clinical characteristics of adult MRSA and MSSA bacteremia patients.

Laboratory data

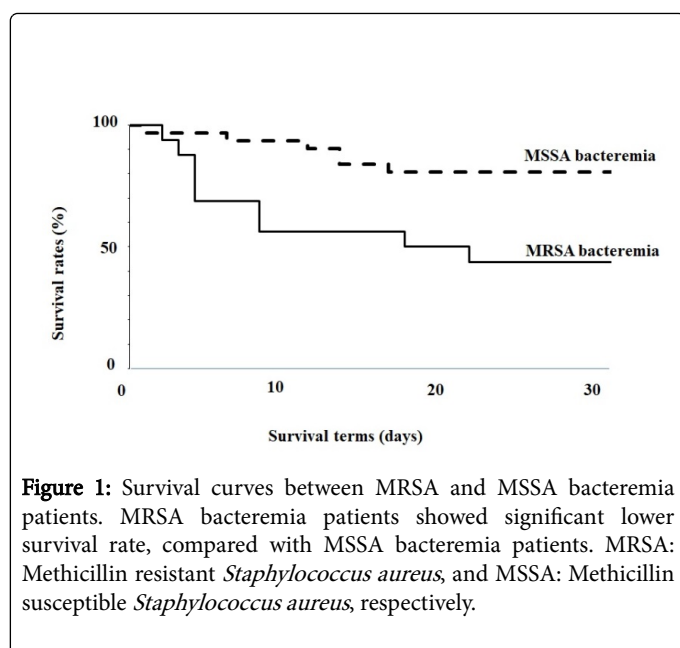
As shown in (Table 2), some laboratory data of MRSA bacteremia patients were significantly worse than those of MSSA bacteremia patients. Inflammatory data (e.g., white blood cell count, C-reactive protein level, and procalcitonin level) and nutritional status (e.g., blood albumin concentration) were almost similar between the MRSA and MSSA groups. However, liver dysfunction data (i.e., Alanine transaminase: ALT, p=0.037) and kidney dysfunction data (i.e., blood urea nitrogen; BUN and creatinine, p=0.001 and p=0.015, respectively) were significantly increased in MRSA bacteremia patients compared with MSSA patients.

	MRSA (n=15)	MSSA (n=30)	p-value
WBC ($\times 10^3/\mu\text{L}$)	13.0 \pm 6.9	10.1 \pm 7.4	p=0.36
Platelet ($\times 10^3/\mu\text{L}$)	172 \pm 146.1	168 \pm 98.0	p=0.46
T-Bil (mg/dL)	1.15 \pm 0.7	0.6 \pm 0.5	p=0.060
AST (U/L)	52.0 \pm 595.6	38.5 \pm 423.6	p=0.059
ALT (U/L)	41.0 \pm 198.7	31.0 \pm 134.5	p=0.037*
LDH (U/L)	347.0 \pm 445.7	291.5 \pm 495.4	p=0.304
BUN (mg/dL)	63.0 \pm 29.0	31.0 \pm 22.6	p=0.001**
Cr (mg/dL)	1.96 \pm 1.17	1.10 \pm 0.24	p=0.015*
Albumin (g/dL)	2.7 \pm 0.7	3.0 \pm 0.9	p=0.21
CRP (mg/dL)	16.1 \pm 12.7	15.9 \pm 11.9	p=0.95
PCT (mg/dL)	5.6 \pm 25.6	1.0 \pm 20.8	p=0.15

Table 2: Laboratory data of adult MRSA and MSSA bacteremia patients.

Patients' outcome

Furthermore, we compared survival rates between MRSA and MSSA bacteremia patients. The 30-day non-survival rates after *Staphylococcus aureus* was isolated from the blood were 60% (9/15 patients) in the MRSA group and 20% (6/30 patients) in the MSSA group (Figure 1).



Mortality was significantly higher with MRSA isolation compared with MSSA isolation (odds ratio: 2.64, 95% CI; 1.806-4.288, $p=0.007$).

Discussion

Bacteremia caused by *Staphylococcus aureus*, especially MRSA bacteremia, is one of the most important problems in infectious disease, resulting in substantial high morbidity and mortality [3,6-10]. Thus, clinical characteristics of MRSA bacteremia should be assessed accurately to select appropriate management and treatments.

We identified 45 adult patients with bacteremia caused by *Staphylococcus aureus* from 2015 to 2018, among which 15 MRSA bacteremia patients were analyzed and compared with 30 MSSA bacteremia patients. MRSA bacteremia patients showed higher mean age and worse laboratory data than MSSA bacteremia patients. Moreover, many MRSA bacteremia patients had diabetes mellitus and liver and renal failure, which were similar to findings in previous reports [8,11,12]. We previously reported that non-survived MRSA bacteremia patients had cardiovascular disease, kidney dysfunction, and poor nutritional status, and complications were caused by lower respiratory tract infections, intravascular devices, and surgical site infections [3]. These data suggested the risk of MRSA bacteremia and the importance of prophylaxis and care of such patients and devices, although we did not find a significant focus of MRSA bacteremia compared with MSSA bacteremia (data not shown).

In addition, we found survival rates were significantly lower in MRSA bacteremia patients compared with MSSA bacteremia patients. These data suggested the difficulty of treating MRSA bacteremia compared with MSSA bacteremia. Although toxicity of MRSA was similar or milder than that of MSSA, anti-MRSA drugs, including vancomycin (VCM), teicoplanin, arbekacin, and daptomycin, required more detailed adjustment of doses and therapeutic drug monitoring to ensure adequate efficiency and low toxicity, as opposed to antibiotics for MSSA, such as penicillins and other beta-lactams [3,13-18]. Additionally, Anti-MRSA drugs may be less effective and/or have more side effects than anti-MSSA drugs. Therefore, the administration of these drugs might also partially explain the higher mortality observed

in MRSA bacteremia compared with MSSA bacteremia. We previously found survival was significantly greater among patients who were the subject of infection control team (ICT) consultation compared with those who were not among MRSA bacteremia cases [3]. Thus, we have recommended treatments and care for not only severe or complicated patients, but also mild to moderate MRSA bacteremia patients. However, those who received ICT consultation were given a range of anti-MRSA drugs more frequently. These results suggested that ICT consultation and the choice of anti-MRSA and other drugs are important for reducing the mortality of MRSA bacteremia patients.

In this study, there was not a significant difference in the trough level of VCM between ICT-positive and -negative patients or between survived and non-survived patients with MRSA bacteremia (data not shown). However, accurate drug loading methods and treatment duration were recently reported in Japanese guidelines of antimicrobial/diagnostic stewardship activity to be as critical [16,17] as exact and non-delayed diagnosis of MRSA bacteremia using appropriate diagnostic methods, including blood culture bottle, PCR, and time-of-flight mass spectrometer (TOF-MS) [19-23].

Conclusion

In conclusion, the outcome of MRSA bacteremia was worse than that of MSSA bacteremia. Higher age, underlying diseases, and kidney and liver dysfunction may be important co-factors responsible for high mortality in MRSA bacteremia patients. Prediction of MRSA and more rapid diagnosis and administration of anti-MRSA drugs could contribute to the improvement of MRSA bacteremia in patients with these characteristics.

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