Title

Influence of antimicrobial regimen on decreased in-hospital mortality of patients with MRSA bacteremia

Running title

Influence of antimicrobial regimen on mortality of MRSA bacteremia

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important causes of bacteremia. Recently, several epidemiological and microbiological changes have become evident in MRSA infections. The purposes of this study were to assess clinical characteristics of patients with MRSA bacteremia and microbiological changes in MRSA. We conducted a retrospective observational study on patients with MRSA bacteremia who were hospitalized between 2008 and 2011. We used univariate and multivariate analysis to evaluate the predictors associated with 30-day mortality. The 7-day and 30-day mortality rates were 12.0% and 25.3%, respectively. According to multivariate analysis, the independent predictors that associated with 30-day mortality were leukopenia, low serum albumin, high sequential organ failure assessment (SOFA) score, and quinolone use within 30 days. Compared to previous data (2003–2007), the SOFA score of the new data set remained unchanged, but in-hospital mortality decreased significantly. In particular, the mortality associated with use of vancomycin (VCM) was significantly lower. Although the minimum inhibitory concentration of VCM required to inhibit the growth of 90% of organisms (MIC_{90}) had not changed, the trough value of VCM changed significantly; a VCM trough value of 10 or greater was significantly higher compared to previous data. Of the staphylococcal cassette chromosome *mec* (SCC*mec*) types, SCC*mec* II values decreased significantly, and SCC*mec* I and IV values increased significantly. Our results indicate that changes in VCM usage might contribute to decreased in-hospital mortality.

Key words: bacteremia, methicillin-resistant *Staphylococcus aureus*, MIC, SCC*mec*, mortality

Introduction

Staphylococcus aureus is one of the most important causes of bacteremia. In the United States, *S. aureus* is the second most common pathogenic cause of bacteremia [1]. In particular, methicillin-resistant *S. aureus* (MRSA) has been detected in 41% of *S. aureus* isolates, and the proportion of MRSA has increased from 22% in 1995 to 57% in 2001 [1]. The in-hospital mortality rate of *S. aureus* bacteremia is approximately 30–40% [2-4], and the 30-day mortality odds ratio of MRSA in comparison to methicillin-sensitive *S. aureus* (MSSA) is 2.15 [5].

Recently, several epidemiological and microbiological changes have become evident with regard to MRSA bacteremia. Community associated (CA)-MRSA strains, typically associated with staphylococcal cassette chromosome *mec* (SCC*mec*) types IV and V and often containing the Panton-Valentine leukocidin (*pvl*) gene, have become widespread in communities [6]; nosocomial infections with CA-MRSA strains also have increased in prevalence [7, 8]. Some reports have indicated that the minimum inhibitory concentration (MIC) of vancomycin (VCM) has increased (MIC creep) [9, 10]. Because of the increase in MIC, a VCM trough value of 10 mg/L or greater has been recommended to inhibit the development of antibiotic resistance [11].

The purpose of this study was to assess clinical characteristics of patients with MRSA bacteremia. Furthermore, we aimed to determine and clarify the epidemiological and microbiological changes in patients with MRSA bacteremia by comparing data obtained in the current study (between 2008 and 2011) with data we had collected previously between 2003 and 2007 [12], which had not exhibited increases in CA-MRSA nor MIC creep.

Materials and methods

Study design and patient population

We conducted a retrospective observational study on patients with MRSA bacteremia who had been hospitalized at Nagasaki University Hospital between January 2008 and December 2011. Patients who were less than 20 years of age were excluded from this study. For patients who developed MRSA bacteremia several times within a 4-year period, only the first episode of MRSA bacteremia was included in the data set.

We investigated baseline characteristics, illness severity, presumed source, antimicrobial regimens, and outcomes. We also evaluated antimicrobial susceptibility, SCC*mec* types, and virulence genes in preserved strains. In addition, we compared non-survivors of MRSA bacteremia to survivors. Finally, we compared the present data set to data we had collected previously from individuals who MRSA bacteremia between January 2003 and December 2007 [12].

We adhered to the Japanese ethical guidelines for epidemiologic studies. The protocol for this study was approved by the ethics committees of Nagasaki University Hospital (No. 12062540).

Definition of bacteremia

In this study, bacteremia was defined as confirmation of 1 or more positive blood cultures from patients exhibiting clinical signs of infection, such as fever, chills, and sweats. When the chief physician described in a medical record as a contamination of MRSA, the patient was excluded from this study. Bacteremia was presumed in patients who presented with typical symptoms and from whom MRSA was isolated prior to the onset of bacteremia. The infection was deemed catheter-related if inflammatory signs were observed at the catheter insertion point and if the catheter culture was MRSA positive. Patients were

diagnosed with MRSA pneumonia if they met the following criteria: (1) isolation of MRSA from sputum, bronchoalveolar lavage, or transthoracic aspiration prior to initial antimicrobial therapy; (2) chest radiographs that are consistent with pneumonia diagnosis; (3) symptoms or signs of pneumonia, such as cough, purulent sputum, abnormal auscultatory findings, signs of respiratory failure, and signs of dyspnea. MRSA bacteremia was classified as community-acquired, healthcare-associated, or hospital-acquired in accordance with the previous report [13].

Assessment of laboratory data and illness severity

In this study, we used vital data and laboratory data that were collected from the patient on the day the patient's blood culture first yielded positive result. Leukopenia was defined as a white blood cell (WBC) count of less than 4,000 /μL. Illness severity was assessed by SOFA score [14].

Identification of bacteria

All *S. aureus* isolates were identified by morphologic analysis of colonies, Gram stain, and the use of the Phoenix bacterial identification system (BD Diagnostics ; Sparks, MD, USA). Isolates were identified as MRSA if the oxacillin MIC was at least 4 μg/mL. The MICs of the preservation strains were measured using a dilution antimicrobial susceptibility test according to the manufacturer's instructions (Eiken Chemical; Tokyo, Japan). The MICs of VCM, teicoplanin (TEIC), arbekacin (ABK), linezolid (LZD), and daptomycin (DAP) were determined after 24 hours of incubation at 35°C.

Real-time PCR assay

DNA extraction and real-time PCR were performed as reported previously [12, 15].

Bacterial DNA was extracted using Chelex (Bio-Rad Laboratories; Hercules, CA, USA), methanol, and boiling methods. Real-time PCR was performed using a LightCycler 480 (Roche Applied Science; Mannheim, Germany) to amplify a total of 10 genes in the same run. Primers and probes were purchased from Nihon Gene Research Laboratories Inc. (Miyagi, Japan).

Data collection 2003–2007

The data collected between 2003 and 2007 was reported previously [12]. In this study, we compared our newly obtained data (2008–2011) with our previously obtained data (2003–2007) to confirm changes in patients with MRSA bacteremia. The previous report did not include VCM trough values and mortality rates in relation to initial antimicrobial therapy; those values were derived newly from the 2003–2007 database.

Statistical analysis

A statistical software package (StatMate IV for Windows®; ATMS Co., Ltd.; Tokyo, Japan) was used to perform statistical comparisons. All comparisons were unpaired and tests of significance were two-tailed. The α-level denoting statistical significance was set to 0.05 or less. Continuous variables were compared using the Student *t*-test if the variables were distributed normally or the Mann-Whitney *U*-test if the variables exhibited non-normal distribution. The chi-square or Fisher's exact test was used to compare categorical variables. Variables with a *P* value less than 0.20 according to univariate analysis were considered for inclusion in the forward stepwise multivariate logistic regression analysis to determine the predictors associated with 30-day mortality. The contribution of each potential risk factor was denoted by the odds ratio (OR) and associated 95% confidence interval (CI).

Results

Patient characteristics

During the study period, we evaluated 83 patients (58 men and 25 women) with MRSA bacteremia comprised of 3 patients with community-acquired bacteremia, 5 patients with healthcare-associated bacteremia, and 75 patients with hospital-acquired bacteremia. Patient characteristics are listed in Table 1. The mean age and body temperature of patients were 67.3 years and 38.8°C, respectively. The severity of MRSA bacteremia was determined based on the mean SOFA score, which was 5.8. A SOFA score of 5 or greater was assigned to 43 (51.8%) patients

A total of 34 (41.0%) patients had a malignancy, but only 8 of those patients had received chemotherapy within 30 days. Of the 83 patients, 33 (39.8%) had cardiovascular disease, 24 (28.9%) had diabetes mellitus, 20 (24.1%) had chronic renal failure, and 18 (21.7%) had a disease of the central nerve system. In contrast, only 10 patients (12.0%) had received immunosuppressive drugs or corticosteroids and 5 patients (6.0%) had a history of transplantation. The presumed sources of infection in patients with MRSA bacteremia are listed in Table 2. The most frequent source of bacteremia was intravascular devices (25 patients, 30.1%) followed by the respiratory tract (17 patients, 20.5%). In addition, the use of antimicrobial agents during the previous 30 days also was investigated (Table 3); carbapenems were used most frequency followed by penicillin. Anti-MRSA agents had been used by 12 (14.5%) of the patients with MRSA bacteremia.

Antimicrobial regimens and MICs

Initial patient antimicrobial regimens and MIC curves are shown in Fig. 1. Some patients were treated with VCM (37 [44.6%]), TEIC (11 [13.3%], or LZD 18 (18 [21.7%]). One patient was treated with VCM and ABK. In addition, 16 (19.4%) were treated with no

anti-MRSA agents. Since use of DAP was started at 2011 in Japan, there was no patient who was treated with DAP. The MICs of the 78 isolates were measured. The MIC_{90} values for VCM, TEIC, ABK, LZD, and DAP were 1, 1.5, 0.75, 4, and 0.75, respectively. Most strains obtained from blood cultures were sensitive to these 5 antimicrobial agents, and VCM MIC creep was not observed.

Genetic analysis

The SCC*mec* and virulence genes were identified in this study. Of the 78 patients, 18 (23.1%) carried SCC*mec* type I, 35 (44.9%) carried SCC*mec* type II, 1 (1.3%) carried SCC*mec* type III, and 24 (30.8%) carried SCC*mec* type IV. With regard to virulence genes, 41 patient isolates (52.6%) tested positive for *tsst*, 38 patient isolates (48.7%) were *sec* positive, and none of the isolates tested positive for either *etb* or *pvl*. Of the 35 patient SCC*mec* type II isolates, 28 (80.0%) were positive for *tsst* and *sec* genes, as were 33.3% (8/24) of the SCC*mec* type IV isolates. None of the SCC*mec* type I isolates tested positive for *tsst* or *sec*. The prevalence of *tsst* and *sec* in SCC*mec* type II isolates was significantly higher that the prevalence of these genes in SCC*mec* types I and IV ($P < 0.001$).

Outcomes and prognostic factors

The 7-, 30-day, and in-hospital mortality rates were 12.0%, 18.1%, and 25.3%, respectively. Predictors associated with 30-day mortality based on univariate and multivariate analysis are shown in Table 4. The univariate analysis included patient characteristics (including vital signs and laboratory data), presumed source of infection, initial antimicrobial regimen, antimicrobial agents that were used within the previous 30 days, MICs of anti-MRSA agents, SCC*mec* types, and virulence genes. This analysis determined that predictors associated with 30-day mortality include hematologic malignancy, respiratory

disease, hepatobiliary disease, leukopenia, low serum albumin (≤2.5 g/dL), and high SOFA scores (≥5 and ≥15). Based on multivariate analysis, the independent predictors associated with 30-day mortality were leukopenia (OR, 31.5; 95% CI, 3.1–322.8; $P = 0.004$), low serum albumin (≤2.5 g/dL) (OR, 14.7; 95% CI, 1.9–116.2; $P = 0.011$), high SOFA score (≥15) (OR, 38.6; 95% CI, 3.5–431.1; $P = 0.011$), and use of quinolones within the previous 30 days (OR, 6.2; 95% CI, 1.0–38.9; $P = 0.050$).

Comparison to 2003–2007 data

To confirm the changes that have developed in MRSA bacteremia, we compared data from this study with data gathered between 2003 and 2007, which we had reported previously [12]. Compared to the previous study, the proportion of male patients was significantly higher and the proportion who received immunosuppressive drugs or corticosteroids was significantly lower in this study (53.0% versus 69.9%; $P = 0.026$ and 30.1% versus 12.0%; $P = 0.004$, respectively). No significant differences were evident between the 2 studies with regard to presumed sources of infection; however, although the proportion of intravascular devices used was higher in this study, the differences were not significant. With regard to SOFA scores, the 2 studies did not differ significantly (6.0 ± 4.5 versus 5.8 ± 4.7; $P = 0.739$). However, the in-hospital mortality rate from this study was significantly lower than in the previous study (39.8% versus 25.3%; $P = 0.047$).

A comparison of the initial antimicrobial regimens and mortality rates based on the initial antimicrobial agents is shown in Table 5. The frequency of VCM use was significantly greater in this study compared to the previous study (26.5% versus 44.6%; $P = 0.015$). In contrast, the frequency of TEIC use was significantly lower in this study (39.8% versus 13.3%; $P < 0.001$). In addition, the rate of mortality based on VCM use was significantly lower in this study (59.1% versus 21.6%; $P = 0.004$). Whereas no changes were observed in

the VCM MIC_{90} between the 2 studies (Table 5), a change was observed in the VCM trough value in patients who received VCM. In this study, the VCM trough value was measured in 59.5% of the patients who had received VCM (22/37); the prevalence of values ≥ 10 was significantly higher compared to the previous study (50.0% versus 76.0%; $P = 0.031$).

With regard to SCC*mec* types, the prevalence of type II was significantly lower in this study compared with the previous study (79.2% versus 44.9%; $P < 0.001$). In contrast, the prevalence of SCC*mec* types I and IV were higher (2.6% versus 23.1%; $P < 0.001$, and 18.2% versus 30.8%; $P = 0.069$) (Fig. 2). The prevalence of *tsst* and *sec* genes was significantly lower in this study (79.2% versus 52.6%; $P < 0.001$ and 76.6% versus 48.7%; $P < 0.001$, respectively) (Fig. 2). The mortality rates based on SCC*mec* types and virulence genes could not be compared between the 2 studies because these data were not available from the previous study. In this study, the 30-day mortality rates for SCC*mec* types I, II, and IV were 11.1%, 22.9%, and 16.7%, respectively. In addition, the 30-day mortality rates based on the presence or absence of virulence genes were 17.0% and 19.0%, respectively. No significant differences were evident in 30-day mortality based on SCC*mec* types and virulence genes.

Discussion

Our results revealed clinical characteristics of patients with MRSA bacteremia and microbiological changes in MRSA. Compared to our previous study [12], several changes in initial antibiotic regimens, SCC*mec* types, and virulence genes had emerged. In contrast, patient characteristics, severity of illness, and MICs did not change significantly. Additionally, in-hospital mortality was significantly decreased in this study compared to the previous study.

With regard to initial antibiotic regimens, the frequency of VCM use had increased significantly and the VCM-based mortality had decreased significantly in this study. Because other antimicrobial agents were not associated with changes in mortality, the changed frequency of VCM use appeared important for decreased mortality. Although the MIC_{90} for VCM had not changed between the 2 studies, the trough value of VCM had changed significantly; the prevalence of patients in this study with a VCM trough value of 10 or greater was significantly higher in this study. In some studies, a VCM trough value less than 10 mg/L may have served as a predictor of therapeutic failure and introduced the possibility that VCM-resistant MRSA would emerge [16, 17]. A VCM trough value of 10 mg/L or greater has been recommended in a consensus review on therapeutic VCM monitoring [11]. Therefore, change VCM usage of VCM may contribute to decreasing in-hospital mortality.

For SCC*mec* types, type II prevalence was significantly lower, and type I and IV prevalence were higher in this study. Worldwide, SCC*mec* type IV, which usually associates with CA-MRSA, has been observed widely—in community-based infections and also in nosocomial infections [7, 8]. In Japan, the historical prevalence of SCC*mec* type IV was approximately 4% in previous studies [18, 19] and has grown to 20.0% according to a recent, nationwide Japanese survey on MRSA [19]. Increases in SCC*mec* type IV occur commonly in Japan and other countries, but exhibit differences among clones. In the United States and

Europe, the most common strain has been the USA300 strain, which carries the *pvl* gene and is the most common CA-MRSA clone. In contrast, the prevalence of the *pvl* gene in CA-MRSA was approximately 2% to 4% in Japan [20, 21]. Thus, most CA-MRSA strains in Japan were not derived from the USA300 strain. In our study, none of the strains carried the *pvl* gene, and it is similar to precious studies in Japan [20, 21]. In addition, SCC*mec* type I also exhibited a significant increase in this study. However, no similar studies have been conducted. Accordingly, further investigation is needed to reveal whether SCC*mec* type I increases temporarily.

The question that followed was whether these changes in SCC*mec* type contributed to decreased in-hospital mortality. In the previous study, the 90-day cumulative probability of survival in patients with MSSA, CA-MRSA, or hospital-associated (HA)-MRSA bacteremia were 71%, 70%, and 55%, respectively; the only association with an increased risk of mortality according to multivariate analysis was observed in patients with HA-MRSA bacteremia in comparison to patients with MSSA bacteremia [22]. Other study showed that the 30-day cumulative survival rate for patients with SCC*mec* types II or IV were 60.0% and 81.8%, respectively [23]. In our study, the 30-day mortality of patients with SCC*mec* type IV was lower than that of patients with SCC*mec* type II, and the 30-day mortality of patients with SCC*mec* type I also was lower than that of patients with SCC*mec* type II. However, the difference was not significant. Therefore, we could not decide whether the changes in SCCmec type contributed to decreased in-hospital mortality. In addition, the changing prevalence of virulence genes did not appear to contribute to decreased in-hospital mortality; the 30-day mortality rate did not change with the presence or absence of virulence genes (17.0% and 19.0%, respectively). It is certain that the prevalence of virulence genes *tsst* and *sec* was significantly lower in this study than in our previous study. However, the changed prevalence may be related to changed SCC*mec* types. In this study, the prevalence of *tsst* and

sec genes in SCC*mec* types I and IV was significantly lower than the prevalence of these genes in SCC*mec* type II. Consequently, the decreased prevalence of SCC*mec* type II led to the decreased prevalence of virulence genes.

In contrast, changes in patient characteristics appear to contribute to decreased in-hospital mortality. Although nearly no changes were observed in patient characteristics in this study, the proportion of patients who received immunosuppressive drugs or corticosteroids was significantly lower than that in the previous study. The use of immunosuppressive drugs or corticosteroids had served as a predictor of in-hospital mortality based on univariate analysis in our previous study, and thus, the lower proportion of patients on these drugs in this study may have contributed to decreased in-hospital mortality. Additionally, transplantation was a predictor associated with mortality based on multivariate analysis in our previous study but not in this study. Although we are unable to provide an apparent explanation for why these patients decreased in this study, we have realized that infection prevention in the immunocompromised host might be effective in our hospital. In our hospital, Infection Control and Education Center was established at 2006, and multidrug-resistant *Pseudomonas aeruginosa* infection decreased after the establishment (data were not shown). Since a previous study reported that received infection control team consultation reduced the mortality of patients with MRSA bacteremia [24], there was some possibility that improvement of infection prevention in the immunocompromised host decreased in-hospital mortality. In comparison with our previous report, use of quinolones within the previous 30 days was the independent predictors associated with 30-day mortality. Quinolones were usually used at combination therapy in critically ill patients, but we could not clarify the causation of quinolones and in-hospital mortality.

In conclusion, this study revealed that changes in VCM usage might contribute to decreased in-hospital mortality. Recently, many studies have been conducted on the

epidemiological and microbiological changes that have developed in MRSA bacteremia, but few of these studies have examined how changes affect in-hospital mortality. Therefore, further investigation is needed to clarify the influence that these changes have on outcomes.

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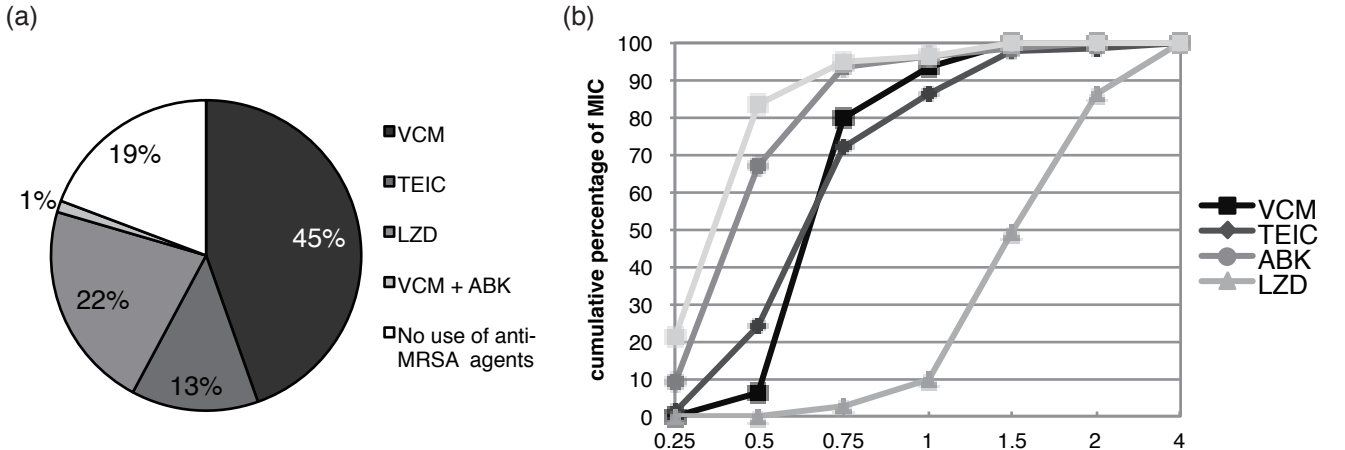

Fig 1. Initial antimicrobial regimens and minimum inhibitory concentration (MIC) curves in patients with MRSA bacteremia

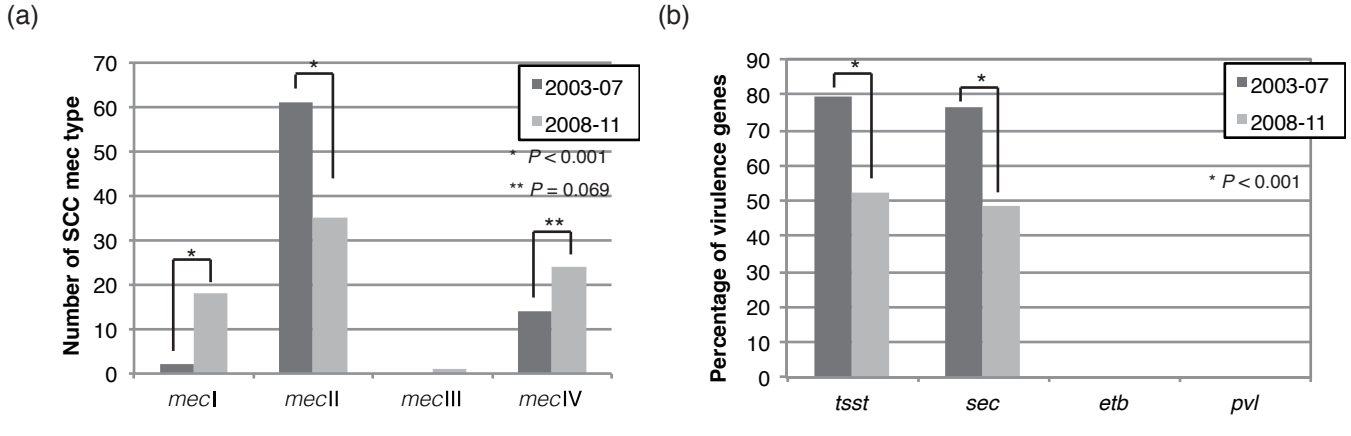

Fig. 2. A comparison of SCCmec types and virulence genes detected during 2 time frames, 2003–2007 and 2008–2011.

Table 1. Patient characteristics of patients with MRSA bacteremia

Sex (male/female)	58/25
Mean age (years)*	67.3 ± 17.0
Classification by the onset place of bacteremia:	
Community-acquired	3 (3.6%)
Healthcare-associated	5 (6.0%)
Hospital-acquired	75 (90.4%)
Underlying disease:	
Malignancy	34 (41.0%)
Hematologic malignancy	6 (7.2%)
Chemotherapy within 30 days	8 (9.6%)
Cardiovascular disease	33 (39.8%)
Diabetes mellitus	24 (28.9%)
Chronic renal failure	20 (24.1%)
Hemodialysis	17 (20.5%)
Central nurve system disease	18 (21.7%)
Respiratory disease	13 (15.7%)
Hepatobiliary disease	13 (15.7%)
Autoimmune/allergic disease	12 (14.5%)
Immunosupressive drugs or corticosteroids use	10 (12.0%)
Physical trauma	9 (10.8%)
Gastrointestinal disease	7 (8.4%)
Tlansplantation	5 (6.0%)
Body temprature (˚C) *	38.7 ± 4.7
SOFA-scorea*	5.8 ± 4.7
SOFA-score ≥ 5	43 (51.8%)

*Values are presented as means ± standard deviations.

Table 2. Presumed source of infection in patients with MRSA bacteremia

Presumed source	Number of patients (%)
Intravascular device	25 (30.1%)
Respiratory tract (patients with pneumonia)	17 (20.5%)
Soft tissue	7 (8.4%)
Surgical wound	6 (7.2%)
Abdominal cavity	4 (4.8%)
Bone	2 (2.4%)
Others	5 (6.0%)
Unknown	17 (20.5%)

Table 3. Antimircrobial agents used within last 30 days

Antimicrobial agents*	Number of patients (%)
Penicillins	21 (25.3%)
1st cefems	16 (19.3%)
2nd cefems	5 (6.0%)
3rd cefems	14 (16.9%)
Carbapenems	27 (32.5%)
Quinolones	14 (16.9%)
Anti-MRSA agents	12 (14.5%)
VCM	6 (7.2%)
TEIC	4 (4.8%)
ABK	1 (1.2%)
LZD	1 (1.2%)
Others	12 (14.5%)
All	63 (75.9%)

*There are some overlapping cases.

Table 4. Univariate and multivariate analysis of predictors associated with 30-day mortality of patients with bacteremia

Predictor	OR (95%CI)	P value
Univariate analysis		
Community-acquired bacteremia	10.3 (0.9 - 122.2)	0.143
Hematologic malignancy	12 (2.0 - 73.6)	0.008
Respiratory disease	5.8 (1.6 - 21.2)	0.013
Hepatobiliary disease	5.8 (1.6 - 21.2)	0.013
History of transplantation	8.3 (1.2 - 54.7)	0.056
Body temperature < 36.0 ˚C	10.3 (0.9 - 122.2)	0.143
Body temperature ≥ 39.0 ˚C, < 40.0 ˚C	2.9 (0.9 - 9.3)	0.111
Leukopenia	8 (1.8 - 34.9)	0.008
serum albumin ≤ 2.0 g/dl	10.3 (0.9 - 122.2)	0.143
serum albumin ≤ 2.5 g/dl	5.8 (1.6 - 20.1)	0.008
serum albumin ≤ 3.0 g/dl	7.6 (0.9 - 61.7)	0.061
SOFA-score ≥ 5	4.8 (1.2 - 18.5)	0.033
SOFA-score ≥ 10	4.4 (1.1 - 16.4)	0.059
SOFA-score ≥ 15	12 (2.0 - 73.6)	0.008
Use of carbapenem within last 30 days	2.9 (0.9 - 9.2)	0.111
Use of quinolones within last 30 days	3.3 (0.9 - 11.8)	0.133
Use of lincomycin within last 30 days	4.6 (1.1 - 19.7)	0.086
Multivariate analysis*		
Leukopenia	31.5 (3.1 - 322.8)	0.004
serum albumin ≤ 2.5 g/dl	14.7 (1.9 - 116.2)	0.011
SOFA-score ≥ 15	38.6 (3.5 - 431.1)	0.003
Use of quinolones within last 30 days	6.2 (1.0-38.9)	0.050

*Predictors with a P value < 0.20 in the univariate analysis were included in forward stepwise multivariate logistic regression analysis.

Table 5. Comparison of initial antimicrobial regimens, mortality, and MIC90 between 2003 - 2007 and 2008 - 2011

Antimicrobial agents	No. of patients (%)		P value
	2003-07 (n=83)	2008-11 (n=83)	
Initial antimicrobial regimens			
VCM	22 (26.5%)	37 (44.6%)	0.015
TEIC	33 (39.8%)	11 (13.3%)	< 0.001
ABK	3 (3.6%)	0 (0.0%)	0.244
LZD	11 (13.3%)	18 (21.7%)	0.152
VCM + ABK	0 (0.0%)	1 (1.2%)	0.316
No use of anti-MRSA agents	14 (16.9%)	16 (19.3%)	0.687
Mortality according to initial antimicrobial agents			
VCM	13/22 (59.1%)	8/37 (21.6%)	0.004
TEIC	11/33 (33.3%)	3/11 (27.3%)	0.709
LZD	3/11 (27.2%)	5/18 (27.8%)	0.690
No use of anti-MRSA agents	6/14 (42.9%)	5/16 (31.3%)	0.699
MIC90*			
VCM	1.00	1.00	
TEIC	0.75	1.50	
ABK	0.75	0.75	
LZD	2.00	4.00	

*The number of strains that were used to measure MIC90 was 77 in 2003-07 and 78 in 2008-11