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ORIGINAL ARTICLE

Impact of vancomycin MIC creep on patients with methicillin-resistant *Staphylococcus aureus* bacteremia

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Bacteremia;
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Minimum inhibitory concentration;
Vancomycin creep

Background/Purpose: To date, vancomycin is still the standard treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, but minimum inhibitory concentration (MIC) creep is becoming a major concern. The aims of this study were to investigate trends in vancomycin use and MIC values over the last decade at our institute and to evaluate the outcomes of bacteremic patients infected with MRSA isolates with reduced vancomycin susceptibility.

Methods: Vancomycin use and density were evaluated using the defined daily doses (DDD) method. Patients with MRSA bacteremia were enrolled retrospectively. Patient demographic data and clinical outcomes were analyzed. The first isolate from each patient was collected for E-testing in order to determine vancomycin MIC. MIC trends were assessed as MIC_{50}, MIC_{90}, and the geometric mean.

Results: Vancomycin use has increased over the last decade. One hundred and forty patients were enrolled and their respective isolates were retrieved, including isolates from 45 patients in 2001, 46 patients in 2005, and 49 patients in 2009. The geometric mean ($\pm$ standard deviation) of the vancomycin MIC for MRSA isolates obtained in 2009 was 1.39 ± 0.30 μg/mL, which is significantly higher than the mean vancomycin MIC obtained in 2001 (1.19 ± 0.34 μg/mL, $p < 0.01$) and 2005 (1.99 ± 0.25 μg/mL, $p < 0.001$). There were no significant differences in terms of the in-hospital mortality rate between patients with MRSA isolates with MICs ≥ 1.5 μg/mL or < 1.5 μg/mL.

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Conclusion: We identified a significant upward trend in the use of vancomycin and its MIC over the last decade. This study shows that patients infected with MRSA isolates with high MICs ($\geq$1.5 μg/mL) do not have a significantly higher mortality rate compared with isolates with low MICs ($<$1.5 μg/mL).

Introduction

Staphylococcus aureus is one of the most common pathogens that leads to severe infections, including skin and soft tissue infections, pneumonia, bacteremia, and endocarditis, either in community settings or hospitals. According to the Taiwan Nosocomial Infections Surveillance (TNIS) database, the proportion of methicillin-resistant *S aureus* (MRSA) isolates among all *S aureus* isolates in intensive care units (ICU) is 78.0%.[1] Patients with MRSA bacteremia have a higher mortality rate and must endure longer hospital stays than those with methicillin-susceptible *S aureus* (MSSA) bacteremia.[2] Infections caused by MRSA are worse than those caused by other pathogens due to the limited choices of antibiotics that are available and the fact that it is difficult to eradicate these strains. The relationship between the failure of vancomycin to treat MRSA and infections has been demonstrated in several studies; the recent emergence of heterogeneous vancomycin-intermediate *S aureus* (hVISA), vancomycin-intermediate *S aureus* (VISA), and vancomycin-resistant *S aureus* (VRSA) poses additional challenges for vancomycin therapy.[3,4]

To date, vancomycin is the conventional and most-used drug for the treatment of MRSA infections. Several studies have reported that the increase in the vancomycin minimum inhibitory concentration (MIC) for treating MRSA is associated with a substantial risk of vancomycin treatment failure and a higher mortality rate.[5–7] Lodise et al observed that patients with MRSA bloodstream infections with elevated vancomycin MICs ($\geq$1.5 μg/mL) had longer durations of bacteremia, higher probabilities of recurrent bacteremia within 60 days after vancomycin discontinuation, and longer hospital stays.[8] Sakoulas et al reported that the likelihood of treatment success is significantly lower in patients with MRSA isolates with a vancomycin MIC of 1–2 μg/mL compared with patients infected by isolates with a vancomycin MIC $\leq$ 0.5 μg/mL.[9] These studies concluded that the progressive increase in vancomycin MICs within a susceptible range represents the "MIC creep" phenomenon that is often associated with MRSA infections.

In this context, several studies have demonstrated an increase in vancomycin MICs over the last several years, but other studies are ambiguous regarding MIC creep.[10–14] Thus, the aim of our study was to evaluate MIC trends in clinical bacteremic MRSA isolates over the last decade in our medical center in northern Taiwan and to compare mortality rates among patients infected by MRSA during this period with MRSA isolates with different MICs.

Materials and methods

Study design and patients

This retrospective study was conducted at Tri-Service General Hospital, a 1,700-bed facility serving as a primary care and tertiary referral center in Taipei, Taiwan. The annual consumption of parenteral vancomycin in our hospital, in terms of daily defined doses (DDD) per 1000 patient-days, during 200–2010 were calculated based on the World Health Organization's definition of 2 g vancomycin as one DDD.[15] A list of patients with MRSA bacteremia in 2001, 2005, and 2009 was retrieved from the hospital's clinical microbiology laboratory databases. All of the identified patients were enrolled, and their medical charts were reviewed. Clinical information was collected, including age, sex, co-morbidities, clinical outcomes, and laboratory information. For patients with several episodes of MRSA bacteremia, only the first episode was enrolled in this study.

Several risk factors were taken into consideration in the analysis and are summarized in Table 1. Renal failure was defined as an elevated serum creatinine level $>$1.5 mg/dL, either acute or chronic. Neutropenia was defined as an absolute neutrophil count $<$500 neutrophils/μL. Septic shock was defined as sepsis-induced hypotension (systolic blood pressure $<$90 mmHg or diastolic blood pressure $<$50 mmHg) that persisted despite adequate fluid resuscitation on the day bacteremia was diagnosed. Prior glycopeptide use was defined as glycopeptide use for at least 24 hours within the previous 30 days.

Microbiological analysis

Only one MRSA isolate per patient was included in the microbiological portion of this study. All isolates were identified using routine bacteriological procedures. Methicillin susceptibility testing was performed using the disk diffusion method, in accordance with the criteria of the Clinical and Laboratory Standards Institute (CLSI).[16] Vancomycin MIC determination was performed using the Etest method, according to the manufacturer's guidelines. A suspension of saline calibrated to the 0.5-McFarland turbidity standard was plated onto Mueller-Hinton agar, onto which Etest strips (AB BIODISK, Solna, Sweden) were applied. The plates were incubated at 35°C for 24 hours. The MIC was interpreted as the zone of inhibition that corresponded to a concentration gradient on the Etest strips, according to the manufacturer's guidelines. Quality control was performed using the CLSI-recommended reference strain (ATCC 29213).[16]

Table 1 Demographic characteristics, clinical presentation, and clinical outcomes of 140 patients with MRSA bacteremia in each study year

Year	2001 ($n = 45$)	2005 ($n = 46$)	2009 ($n = 49$)	p-value
Age (y)	65.2 ± 17.5	69.1 ± 19.0	72.9 ± 17.8	0.11
Male sex, *n (%)*	26 (57.8)	35 (76.1)	30 (61.2)	0.15
Co-morbidity, *n* (%)				
Diabetes mellitus	31 (68.9)	28 (60.9)	25 (51.0)	0.21
Surgery within previous 30 d	26 (57.8)	25 (54.4)	19 (38.8)	0.14
Renal failure	14 (31.1)	22 (47.8)	20 (40.8)	0.26
Solid neoplasm	13 (28.9)	6 (13.0)	13 (26.5)	0.148
Congestive heart failure	11 (24.4)	11 (23.9)	8 (16.3)	0.56
Dementia	5 (11.1)	8 (17.4)	12 (24.5)	0.24
Neutropenia	5 (11.1)	2 (4.4)	2 (4.1)	0.30
Hematological neoplasm	5 (11.1)	0 (0.0)	4 (8.2)	0.08
Chronic obstructive Pulmonary disease	3 (6.7)	8 (17.4)	3 (6.1)	0.13
Valvular heart disease	3 (6.4)	7 (15.2)	5 (10.2)	0.42
Alcoholism	2 (4.4)	1 (2.2)	2 (4.1)	0.82
Liver cirrhosis	2 (4.4)	3 (6.5)	5 (10.2)	0.55
Community-onset infection	20 (44.4)	14 (30.4)	24 (49.0)	0.16
Receipt of empirical glycopeptide	18 (40.0)	17 (37.0)	20 (40.8)	0.92
Glycopeptide use within previous 30 d	4 (8.9)	9 (19.6)	15 (30.6)	0.03
Septic shock	22 (48.9)	20 (43.5)	22 (44.9)	0.89
In-hospital mortality	19 (42.2)	16 (34.8)	22 (44.9)	0.59

Statistical analysis

Comparisons of the contingency data obtained for each study group were carried out using the χ^2 test or the Fisher's exact test, while comparisons of continuous data were performed using one-way analysis of variation (ANOVA) or the Student t test. Variables with two-tailed $p < 0.05$ were considered statistically significant. Pearson's χ^2 test was used for comparisons of vancomycin usage in our hospital. In order to identify the risk factors associated with mortality, univariate analysis was first conducted. Variables with a $p < 0.05$ were then analyzed using multivariate analysis. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

The annual consumption of parenteral vancomycin in our hospital (in terms of DDD per 1000 patient-days) was 9.06 in 2003, 9.22 in 2004, 10.92 in 2005, 9.50 in 2006, 9.86 in 2007, 9.85 in 2008, 13.47 in 2009, and 13.05 in 2010. Fig. 1 shows the increase in annual intravenous vancomycin use density from 2003—2010 (earlier data could not be obtained due to a shift in the hospital information system). The annual consumption of parenteral vancomycin in our hospital was 10.92 in 2005 and 13.47 in 2009, a statistically significant difference ($p = 0.001$).

During the study years, a total of 140 patients with MRSA bacteremia were enrolled for analysis, including 45 patients in 2001, 46 in 2005, and 49 in 2009. The demographic and clinical characteristics of these patients are summarized in Table 1. The mean age was 65.2 ± 17.5 years in 2001, 69.1 ± 19.0 in 2005, and 72.9 ± 17.8 in 2009. The percentage of male patients that were treated was 57.8% in 2001, 76.1% in 2005, and 61.2% in 2009.

The use of intravascular catheters in this study included 37 cases of central venous catheters, 17 cases of double lumen catheters, and 6 cases of Swan-Ganz catheters. All cases of neutropenia resulted from sepsis; none were related to postchemotherapy neutropenia. Surgery within the first 30 days was defined as a major surgery if either general or local anesthesia was used; this mainly included 13 surgeries for debridement, 10 for percutaneous creation of arteriovenous shunts, 9 for tracheostomy, and 4 for Hickman catheter implantation. Empirical glycopeptides

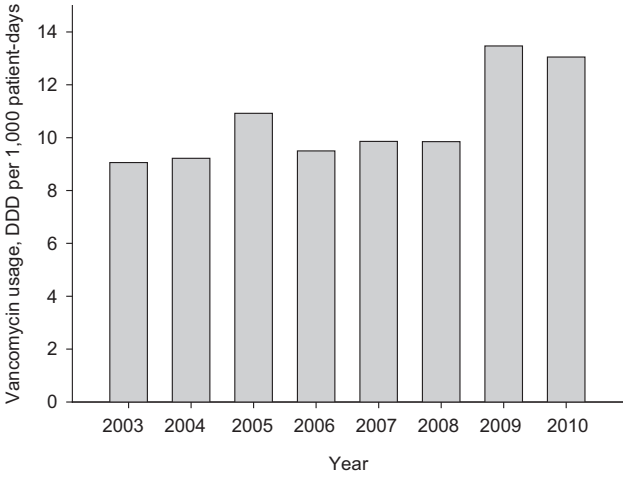

Figure 1. Annual intravenous vancomycin usage density, 2003-2010. One daily dose of vancomycin was defined as 2 g.

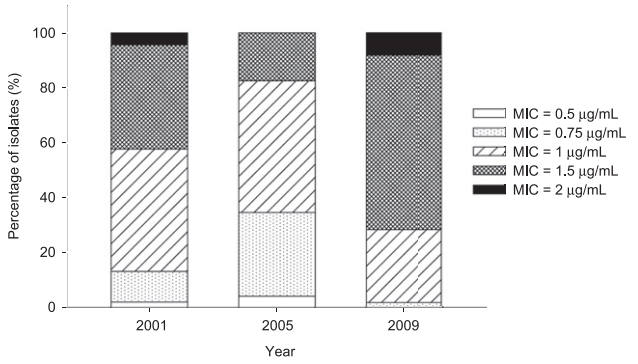

Figure 2. Percentage of 140 bacteremic MRSA isolates with different vancomycin MICs.

were used in 55 of the 140 episodes of MRSA bacteremia, including 45 uses of vancomycin. There were no significant differences across the 3 years of this study in terms of patient age, sex, co-morbidities, community-acquired infections, empirical glycopeptides use, septic shock, or in-hospital mortality.

All 140 documented *S aureus* strains were susceptible to vancomycin, exhibiting MICs below the current CLSI breakpoint (2 μg/mL).[16] The vancomycin MICs for each study year are shown in Fig. 2. A decrease was observed in the number of strains with MICs < 1.5 μg/mL (57.8% in 2001 vs. 28.6% in 2009); a complementary increase was noted for the number of strains with MICs ≥ 1.5 μg/mL (42.22% in 2001 vs. 71.43% in 2009).

The MIC_{50} among blood isolates in 2009 was 1.5 μg/mL, while an MIC_{50} of 1.0 μg/mL among blood isolates was found in 2001 and 2005. The MIC_{90} among blood isolates across the entire 3 years of this study was 1.5 μg/mL. The geometric means ± standard deviations for the vancomycin MICs were 1.19 ± 0.34 μg/mL in 2001, 0.99 ± 0.27 μg/mL in 2005, and 1.39 ± 0.30 μg/mL in 2009, with the last year exhibiting a significant increase compared with 2001 ($p = 0.008$) and 2005 ($p < 0.001$). Statistics for MRSA vancomycin MIC obtained for each study interval, including the geometric mean, MIC_{50}, and MIC_{90}, are shown in Table 2. Vancomycin MICs demonstrated a clear shift over the course of this study.

Comparisons of the clinical features and outcomes between the low (< 1.5 μg/mL) and high (≥ 1.5 μg/mL) vancomycin MIC groups, and between death and survival rates (i.e., in-hospital mortality), are shown in Table 3. We found that patients infected with strains with elevated MICs (≥ 1.5 μg/mL) were strongly associated with the initial presentation of septic shock ($p < 0.05$) and the use of glycopeptides within the 30 days preceding the isolation of a positive culture ($p = 0.02$). Comparisons of the in-hospital mortality rates among patients harboring isolates with different MICs revealed no significant differences ($p = 0.54$).

Univariate analysis determined that the use of an intravascular catheter ($p = 0.01$) and septic shock ($p < 0.05$) are risk factors for in-hospital mortality. Multivariate analysis determined that septic shock is the only independent factor associated with MRSA bacteremia (OR, 25.75; 95% CI: 8.36—79.33). All statistical results are shown in Table 4.

Discussion

In this study, we calculated the vancomycin usage density (in terms of DDD) per 1000 patient-days; this parameter revealed an increase in the usage density, especially in 2009—2010. We observed a shift in the MICs of vancomycin over the same interval. Our results contrast those of Alos et al, who reported no vancomycin MIC creep from 2002—2006 in a setting with a low usage of vancomycin (Spain); no increase in vancomycin density was found in the years of their study.[13] Due to the recent discovery of decreased clinical efficacy and therapeutic response to vancomycin, the Infectious Diseases Society of America (IDSA) recommended an adjustment in the target vancomycin trough level to 15—20 μg/mL for serious MRSA infections in 2009.[17,18] This could be the reason why the vancomycin usage density increased in our hospital.

Most surveillance studies have recently reported changes in vancomycin susceptibility[10—12,19]; however, some studies examining vancomycin MIC creep in MRSA isolates have shown inconsistent results.[13,14] In this study, we demonstrated the existence of the vancomycin creep phenomenon for bacteremic MRSA isolates in our hospital across 3 years (2001, 2005, and 2009). We used the Etest method to determine vancomycin MICs and also employed frequency distributions and geometric mean analyses to demonstrate shifts in vancomycin MICs in MRSA blood isolates. Our data demonstrate a clear and significant difference in vancomycin MICs in our hospital across the 3 years that were studied. There are several other studies that investigated this MIC creep phenomenon, some of which are consistent with our observations.[10—12,19] A 20-year study conducted in a large French teaching hospital demonstrated decreased susceptibility to glycopeptides in MRSA.[19] Steinkraus et al reported that the MICs for oxacillin, vancomycin, and linezolid increased in clinical MRSA isolates from 2001—2005 at a tertiary care institution

Table 2 Statistics on MRSA-vancomycin MICs for each year studied

Year	Number of strains	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC < 1.5 μg/mL, n (%)	MIC ≥ 1.5 μg/mL, *n* (%)	Geometric mean (μg/mL)
2001	45	1	1.5	26 (57.8)	19 (42.2)	1.19 ± 0.34
2005	46	1	1.5	38 (82.6)	8 (17.4)	0.99 ± 0.27
2009	49	1.5	1.5	14 (28.6)	35 (71.4)	1.39 ± 0.30

MIC: minimum inhibitory concentration.

Table 3 Comparisons of clinical features and outcomes between low (<1.5 μg/mL) and high (≥1.5 μg/mL) vancomycin MIC groups and comparisons between death and survival (in-hospital mortality)

	Low MIC	High MIC	*p*-value	In-hospital mortality		*p*-value
	(<1.5 μg/mL)	(≥1.5 μg/mL)		Survival	Death	
	(*n* = 78)	(*n* = 62)		(*n* = 83)	(*n* = 57)	
Male sex, *n* (%)	51 (65.4)	40 (64.5)	1	53 (63.9)	38 (66.7)	0.73
Age, mean y ± SD	68.4 ± 18.2	70.2 ± 17.3	0.55	68.3 ± 17.9	70.5 ± 17.7	0.46
Co-morbidity, *n* (%)						
Intravascular catheter	40 (51.3)	40 (65.4)	0.12	40 (48.2)	40 (70.2)	0.01
Surgery within previous 30 d	37 (47.4)	33 (53.2)	0.61	44 (53)	26 (45.6)	0.39
Diabetes mellitus	34 (43.6)	33 (53.2)	0.31	45 (54.2)	22 (38.6)	0.69
Renal failure	31 (39.7)	25 (40.3)	1	33 (39.8)	23 (40.4)	0.94
Valvular heart disease	10 (12.8)	5 (8.1)	0.42	6 (7.2)	9 (15.8)	0.11
Heart failure	17 (21.8)	13 (21.0)	1	14 (16.9)	16 (28.1)	0.11
Solid neoplasma	17 (21.8)	15 (24.2)	0.84	16 (19.3)	16 (28.1)	0.22
Chronic obstructive pulmonary disease	10 (12.8)	4 (6.5)	0.26	11 (13.3)	3 (5.3)	0.12
Dementia	9 (11.5)	16 (25.8)	0.04	17 (20.5)	8 (14)	0.32
Liver cirrhosis	8 (10.3)	2 (3.2)	0.19	5 (6)	5 (8.8)	0.19
Hematological neoplasma	3 (3.8)	6 (9.7)	0.18	3 (3.6)	6 (10.5)	0.1
Alcoholism	2 (2.6)	3 (4.8)	0.66	2 (2.4)	3 (5.3)	0.37
Bone marrow transplantation	0 (0.0)	2 (3.2)	0.19	2 (2.4)	0 (0)	0.24
Glycopeptide use within previous 30 d	10 (12.8)	18 (29.0)	0.02	69 (83.1)	43 (75.4)	0.26
Septic shock	30 (38.5)	34 (54.8)	<0.05	17 (20.5)	47 (82.5)	<0.05
In-hospital mortality	30(38.7)	27(43.55)	0.54			
MIC ≧ 1.5 μg/mL				35 (42.17)	27 (47.37)	0.54

MIC: minimum inhibitory concentration.

in the USA. [10] In another recent study, Ho et al reported vancomycin MIC creep among MRSA isolates in a region of Hong Kong from 1997–2008.[12] However, in another study, the SENTRY Antimicrobial Surveillance Program reported no evidence of increased vancomycin resistance during 1998–2003 when vancomycin MICs were analyzed.[20] Musta et al demonstrated that the vancomycin MIC distribution was stable over an 11-year span from 1996–2006.[21] Kehrmann et al examined bloodstream MRSA isolates at several hospitals in two German cities between 2004–2009. That study concluded that the creep phenomenon seems to vary by region.[14] Different observations in these vancomycin MIC creep-associated studies may be due to differences in the study periods, geographic locations, vancomycin usage densities, number of enrolled cases, and MIC assays that were employed (e.g., Etest, microdilution, or automated methods).

Table 4 Factors independently associated with mortality as determined using a logistical regression model of patients with MRSA bacteremia

Factor	OR (95% CI)	*p*-value
Diabetes melllitus	0.48 (0.15–1.54)	0.22
Valvular heart disease	2.13 (0.34–13.38)	0.42
Surgery within previous 30 d	0.60 (0.22–1.64)	0.32
Alcoholism	0.96 (0.09–10.43)	0.97
Dementia	0.29 (0.07–1.16)	0.08
Liver cirrhosis	1.77 (0.32–9.93)	0.52
Heart failure	1.09 (0.25–4.76)	0.91
Renal failure	0.64 (0.20–4.76)	0.46
Chronic obstructive pulmonary disease	0.98 (0.17–5.53)	0.98
Solid neoplasm	1.69 (0.53–5.34)	0.37
Hematologic neoplasm	3.02 (0.21–43.58)	0.42
Prior glycopeptides use in 30 d	0.42 (0.10–1.69)	0.22
Intravascular catheter	0.40 (0.14–1.16)	0.09
Septic shock	25.75 (8.36–79.33)	<0.05
MIC ≧ 1.5 μg/mL	0.87 (0.50–1.51)	0.62

MIC: minimum inhibitory concentration; OR: odds ratio; CI: confidence interval.

For the primary outcome analysis, we compared the initial clinical presentation (e.g., shock) and clinical outcome (i.e., in-hospital mortality) between low (<1.5 μg/mL) and high (≥ 1.5 μg/mL) MIC isolates. Our results are similar to those of Lodise et al, who reported no significant difference in mortality,[8] and Soriano et al, who noted that a higher MIC does not correlate with a higher probability of a patient going into shock. In contrast, Wang et al reported higher mortality rates among patients infected with MRSA strains with elevated MICs,[7] which is not consistent with our observations. Among the present study's patients who had used glycopeptides during the preceding 30 days, a larger proportion of patients were infected with isolates with high (≥ 1.5 μg/mL) MICs ($p = 0.017$), as noted by Lodise et al.[22] Indeed, patients with MRSA bacteremia who have been recently treated with vancomycin are known to exhibit reduced susceptibility to this antibiotic, and alternative therapy is recommended for

such individuals if an optimal treatment response is not obtained.

Our study has some limitations. First, this was a retrospective and single-center study, and we did not analyze clonal transmission patterns among MRSA isolates; we did not know the exact clonal prevalence or changes that occurred over time at our local institution. Second, for the comparison of clinical outcomes and MIC, we included only in-hospital mortality and excluded microbiologic failure and recurrence after anti-MRSA treatment. While this approach is consistent with the work of Lodise et al,[8] we did not observe the same influence on higher MIC levels as that analysis. Third, we used the Etest method, rather than the broth microdilution method, to determine vancomycin MICs; the two techniques have been reported to yield MIC values that differ by up to two-fold.[23] Fourth, the vancomycin trough level of each MRSA infection could not be retrieved in our study. Vancomycin therapeutic guidelines from IDSA recommended keeping trough serum vancomycin concentrations at 15–20 μg/mL in order to achieve a targeted AUC/MIC $>$ 400 for most patients, assuming the MIC is $<$ 1 μg/mL.[18] That might be the reason why we couldn't determine the influence of higher vancomycin MICs on mortality in this study.

In conclusion, we detected the occurrence of the vancomycin MIC creep phenomenon in our hospital during three study periods. This event overlapped with an increase in the vancomycin usage density (in terms of DDD per 1000 patient-days), which rose from 2003–2010. Our study also observed that vancomycin usage in the 30 days prior to isolation of a positive culture did positively correlate with higher MICs; in addition, we did not observe an increase in in-hospital mortality among patients infected with higher-MIC isolates. Septic shock was the only independent factor associated with in-hospital mortality, as determined by multivariate analysis. Similar to IDSA's recommendation for the treatment of MRSA infections,[17] we suggest continued vancomycin use to treat MRSA infections if the vancomycin MIC is below 2 μg/mL, while alternative treatments should be considered if a clinical or microbiologic response to vancomycin is not achieved. All medical institutions should monitor their local vancomycin MICs for MRSA isolates in order to help understand resistance among *Staphylococcus* species that is now commonplace.

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