—Regular Article—

Possibility of Poor Outcomes after Treatment Using Teicoplanin at the Minimum Inhibitory Concentration of >2 μg/mL in Methicillin-resistant *Staphylococcus aureus* Bacteremia

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Only minimal information exists regarding the treatment outcomes of patients suffering from methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia treated with teicoplanin (TEIC) when the TEIC minimum inhibitory concentration (MIC) is close to the upper limit of the ''susceptibility range'' according to the Clinical Laboratory Standards Institute (CLSI). We investigated the outcome of TEIC-treated patients in MRSA bacteremia, focusing on TEIC MIC against MRSA. A retrospective cohort study was conducted on patients with MRSA bacteremia. TEIC treatment failure was defined as any of the following: (1) all-cause 60-day mortality, (2) persistent bacteremia until the end of TEIC treatment, or (3) 30-day recurrence of MRSA bacteremia. Nineteen patients were enrolled, of whom 15 exhibited TEIC MICs ≤2 μg/mL and the remaining 4 exhibited >2 μg/mL. The rate of treatment failure and all-cause 60-day mortality in patients with MIC >2 μg/mL were significantly higher than those in patients with MIC ≤2 μg/mL [4 patients (100%) *versus* 4 patients (26.7%) ($p=0.018$) and 4 patients (100%) *versus* 2 patients (13.3%) ($p=0.004$), respectively]. Three of four patients (75%) with MIC >2 μg/mL had persistent bacteremia, which was quantitatively higher than in patients with MIC ≤2 μg/mL (1 of 7 patients, 14.3%). Our finding suggests that TEIC MIC >2 μg/mL may be related to poor treatment outcome in MRSA bacteremia, and that TEIC should not be used in this case.

Key words——teicoplanin; methicillin-resistant *Staphylococcus aureus*; bacteremia

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen involved in hospital-acquired infections, and there are growing concerns about its prevalence worldwide, including Japan.[1–7] Moreover, MRSA bacteremia is known to be associated with a high mortality rate.[1–7]

Teicoplanin (TEIC), a glycopeptide, is an anti-MRSA antibiotic that has been used worldwide (except in the U.S.).[8–13] TEIC has advantages over vancomycin (VCM), the first-line glycopeptide antibiotic against MRSA infections, in terms of low nephrotoxicity and once-daily dosing.[8,9,14] Several studies have reported that VCM minimum inhibitory concentrations (MICs) have increased in recent years, and that a VCM MIC of 2 μg/mL has been associated with treatment failure,[1–4] although VCM MICs ≤2 μg/mL are within the ''susceptibility range'' as designated by the Clinical Laboratory Standards Institute (CLSI) standard, which is used worldwide.[15] In Japan, the CLSI standard is used in most institutions,[16] including our hospital.

CLSI has suggested that the susceptibility range of TEIC MIC for MRSA is ≤8 μg/mL.[15] However, another susceptibility standard, the European Committee on Antimicrobial Susceptibility Testing (EUCAST), which has been used mainly in Europe, has suggested that the susceptibility breakpoint of TEIC MIC for MRSA is 2 μg/mL,[17] which is one-quarter of the breakpoint suggested by CLSI.[15,17,18] This is not just in the case of TEIC; for many antibiotics, the susceptibility breakpoints in EUCAST are restricted compared to those in CLSI.[16] While the breakpoints designated by EUCAST are based on pharmacokinetic-pharmacodynamic (PK-PD) studies, those designated by CLSI are based on *in vitro* data; alternatively, CLSI develops preliminary breakpoints based on PK-PD parameters.[15,17,19,20] Therefore, the breakpoints set by CLSI and EUCAST vary

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widely.

Despite differences in the suggested susceptibility ranges in terms of TEIC MIC between the CLSI (MIC $\leq 2\,\mu g/mL$) and EUCAST (MIC $\leq 8\,\mu g/mL$) standards, little is known about the difference in treatment outcome using TEIC with low and high MICs. The difference between the CLSI- and EUCAST-designated MIC susceptibility ranges (MIC ≤ 2 and $\leq 8\,\mu g/mL$) is large; therefore, clarification of the relationship between treatment outcomes and MICs in the range from MICs ≤ 2 to $8\,\mu g/mL$ is needed to aid clinical decision-making as to whether TEIC is applicable to patients suffering from MRSA bacteremia.

A recent study found that patients with a higher TEIC MIC ($>1.5\,\mu g/mL$) exhibited poorer outcomes compared to those with a lower TEIC MIC ($\leq 1.5\,\mu g/mL$).[21] However, despite the suggestion that TEIC trough levels are associated with clinical outcomes in several studies,[22–27] this was not investigated in the recent study cited above.[21] Therefore, the relationship between the TEIC trough values and the outcomes of that study remains unknown. Furthermore, there was no information as to whether the higher TEIC MIC group ($>1.5\,\mu g/mL$) encompasses patients with MIC $>8\,\mu g/mL$ or not.[21]

This study aimed to clarify the treatment outcomes of patients who received TEIC against MRSA bacteremia, focusing on TEIC MIC within the CLSI-designated susceptibility range (from MICs ≤ 2 to 8 $\mu g/mL$) in consideration of TEIC trough levels.

METHODS

Study Design and Population This retrospective cohort study was conducted at Hokkaido University Hospital, a 936-bed tertiary care medical center, located in Sapporo, Japan. The study protocol was approved by the institutional review board at the hospital. Patients with MRSA bacteremia from April 2008 to Jun 2014 were eligible for inclusion if they fulfilled the following criteria: (1) at least one positive blood culture for MRSA, (2) treatment with TEIC for >2 d (3) no treatment with any other anti-MRSA antibiotic(s) for >48 h before TEIC therapy after the onset of bacteremia, and (4) ≥ 18 years of age.

Patients were administered TEIC 200–600 mg twice per day for 2 d as loading doses, then 200–600 mg once a day as maintenance doses; doses were adjusted based on trough blood TEIC levels and renal function to achieve target trough levels of 15–25 $\mu g/mL$. TEIC trough levels were determined from days 4–7 after initiating TEIC treatment, except for one patient whose level was determined at day 16 after the initiation of treatment. Trough levels obtained during hemodialysis were excluded from this study.

TEIC treatment failure, the primary end point, was defined as any of the following: (1) all-cause 60-day mortality after the onset of bacteremia, (2) persistent bacteremia until the end of TEIC treatment, or (3) recurrence of MRSA bacteremia within 30 d of the end of TEIC treatment.[1–3] The patients' backgrounds, including renal function, intensive care unit (ICU) admission at the onset of bacteremia, history of surgery within previous 30 d from the onset of bacteremia, epidemiologic source (community- or hospital-acquired or healthcare-associated),[28] comorbidities, and potential sources of bacteremia were extracted from medical chart data. Severity of the illness was evaluated using the Sequential Organ Failure Assessment (SOFA) score.[29,30]

Microbiological Methods During the study period, isolates from blood cultures were identified as *S. aureus* according to standard methods. Susceptibility testing for oxacillin resistance was determined according to CLSI guidelines.[15] TEIC MICs were determined using the turbidity standard technique. A sample of individual colonies was suspended in 3 mL of inoculum water to create a 0.5 McFarland turbidity standard. Next, $120\,\mu L$ of the standardized suspension was added to a prompt bottle and mixed. The resulting emulsion of bacteria was analyzed to determine MIC (≤ 2, 4, 8, or $16\,\mu g/mL$) using a MicroScan WalkAway plus System (Beckman Coulter, Tokyo).

Statistical Analysis Categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney *U* test. p values <0.05 were considered statistically significant. All calculations were performed using JMP pro version 12 (SAS Institute Inc., Tokyo).

RESULTS

During the study period, 87 patients exhibited MRSA bacteremia, and 21 of these patients received TEIC for >72 h as an initial therapy after the onset of bacteremia. Two patients were less than 18 years of age, and therefore, 19 patients were enrolled in the study. Fifteen of the enrolled patients had TEIC

Table 1. Comparison of Main Clinical Characteristics between Patients with TEIC MICs $\leq 2\,\mu g/mL$ and $>2\,\mu g/mL$

Characteristic	MIC ≤ 2 ($\mu g/mL$) ($n=15$)	MIC >2 ($\mu g/mL$) ($n=4$)	p value
Age, years	66 (23–84)	63 (26–77)	0.764
Gender, male	10 (66.7)	0 (0)	0.033
Body weight (kg)	59.1 (35.6–64)	52.7 (41.7–56.1)	0.395
BMI (kg/m^2)	18.9 (15.4–30.8)	22.8 (18.1–27)	0.367
Creatinine clearance (mL/min)	60.3 (19.3–174.3)	42.2 (13.9–136.4)	0.342
Hemodialysis	1 (6.67)	1 (25)	0.386
ICU at the onset of bacteremia	1 (6.67)	1 (25)	0.386
Surgery within previous 30 d	5 (33.3)	2 (50)	0.603
SOFA score	3 (0–7)	10.5 (6–11)	0.005
Epidemiologic source			
Community-acquired	0 (0)	0 (0)	
Hospital-acquired	15 (100)	4 (100)	
Healthcare-associated	0 (0)	0 (0)	
Comorbidity			
Diabetes mellitus	2 (13.3)	2 (50)	0.178
Cardiovascular disease	7 (46.7)	3 (75)	0.582
Stroke	3 (20)	1 (25)	1
Renal failure (creatinine >1.5 mg/dL)	4 (26.7)	2 (50)	0.557
Liver cirrhosis	0 (0)	0 (0)	
COPD	0 (0)	0 (0)	
Solid tumor	5 (33.3)	1 (25)	1
Hematological malignancy	8 (53.3)	2 (50)	1
Chemotherapy within 30 d	3 (20)	0 (0)	1
Neutropenia (ANC $<500\ mm^3$)	0 (0)	1 (25)	0.21
Infective endocarditis	0 (0)	0 (0)	
Sepsis	7 (46.7)	2 (50)	1
Transplantation (solid)	0 (0)	0 (0)	
HIV	0 (0)	0 (0)	
Sources of infection			
Catheter-related	4 (26.7)	0 (0)	0.53
Respiratory tract	5 (33.3)	2 (50)	0.603
Skin/wound	4 (26.7)	0 (0)	0.53
Endocarditis	0 (0)	0 (0)	
Bone and joint	0 (0)	0 (0)	
Intra-abdominal	0 (0)	0 (0)	
Urinary tract	0 (0)	0 (0)	
Other site	0 (0)	1 (25)	0.211
Unknown primary site	2 (13.3)	1 (25)	0.53
TEIC trough level in plasma ($\mu g/mL$)[a]	17.5 (6.92–23.7)	13.4 (7.45–27.0)	0.8

[a] TEIC trough levels ($n=9$ for MIC $\leq 2\,\mu g/mL$ and $n=3$ for MIC $>2\,\mu g/mL$) were compared. Data are presented as number (%) or median (range). p values were determined using Mann-Whitney U test for continuous data or Fisher's exact test for categorical data. Abbreviations: ANC, absolute neutrophil count; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; MIC, minimum inhibitory concentration; SOFA, Sequential Organ Failure Assessment; TEIC, teicoplanin.

MICs $\leq 2\,\mu g/mL$, and 4 had $>2\,\mu g/mL$ (2 had MIC $=4\,\mu g/mL$, and 2 had MIC $8\,\mu g/mL$), all of which were determined ''susceptible'' according to the CLSI standard.

Comparison of the main clinical characteristics between patients with TEIC MICs $\leq 2\,\mu g/mL$ and $>2\,\mu g/mL$ is shown in Table 1. There were no significant differences between these groups based on age, body weight, body mass index (BMI), creatinine clearance, percentage of patients receiving hemodialysis, ICU admission at the onset of bacteremia, surgery within the previous 30 d, and comorbidities. The median SOFA score in patients with MIC $>2\,\mu g/mL$ was significantly higher than that in patients with MIC ≤ 2

Table 2. Comparison of Outcomes between Patients with TEIC MICs $\leq 2\,\mu g/mL$ and $>2\,\mu g/mL$

	MIC ≤ 2 ($\mu g/mL$)	MIC >2 ($\mu g/mL$)	p value
Treatment failure[a]	4/15 (26.7)	4/4 (100)	0.018
All-cause 60-day mortality	2/15 (13.3)	4/4 (100)	0.004
Persistent bacteremia	1/7 (14.3)	3/4 (75)	0.088
30-day recurrence of bacteremia	1/4 (25)	1/1 (100)	0.4

[a] TEIC treatment failure, the primary end point, was defined as a composite of all-cause 60-day mortality, persistent bacteremia, and/or 30-day recurrence of MRSA bacteremia. Data are presented as number of patients /total number (%). p values were determined using Fisher's exact test. Abbreviations: MIC, minimum inhibitory concentration; TEIC, teicoplanin.

$\mu g/mL$ [10.5 (range, 6–11) *versus* 3 (range, 0–7), respectively; $p=0.005$]. The ratio of males to females was significantly higher in patients with MIC $\leq 2\,\mu g/mL$ (males/females=10/5) than in those with MIC $>2\,\mu g/mL$ (males/females=0/4). All 19 patients had hospital-acquired infections. There were no significant differences between the two groups in terms of sources of infections. Patients with MIC $\leq 2\,\mu g/mL$ had catheter-related (4/15, 26.7%), respiratory tract (5/15, 33.3%), or skin/wound (4/15, 26.7%) infections. Patients with MIC $>2\,\mu g/mL$ had respiratory tract (2/4, 50%) or other site(s) infections (1/4, 25%). TEIC trough levels were determined for 13 patients (68.4%), excluding 1 patient with hemodialysis. The median level of the initial trough was 17.5 $\mu g/mL$ (range, 6.92–23.7 $\mu g/mL$) and 13.4 $\mu g/mL$ (range, 7.45–27.0 $\mu g/mL$) in patients with MICs $\leq 2\,\mu g/mL$ and $>2\,\mu g/mL$, respectively (not statistically significant; $p=0.8$).

Univariate analyses of treatment outcomes between patients with MIC $\leq 2\,\mu g/mL$ and those with MIC $>2\,\mu g/mL$ are shown in Table 2. Eight patients (42.1%) exhibited treatment failure. Frequency of treatment failure in patients with MIC $>2\,\mu g/mL$ was significantly higher than that in patients with MIC $\leq 2\,\mu g/mL$ [4 of 4 patients (100%) *versus* 4 of 15 patients (26.7%), respectively; $p=0.018$]. Six patients (31.6%) died within 60 d after the onset of bacteremia. Sixty-day mortality in patients with MIC $>2\,\mu g/mL$ was significantly higher than that in patients with MIC $\leq 2\,\mu g/mL$ [4 of 4 patients (100%) *versus* 2 of 15 patients (13.3%), respectively; $p=0.004$]. Persistent bacteremia was evaluated in 11 patients (57.9%) who had blood culture for evaluation. Three of four patients (75%) with MIC $>2\,\mu g/mL$ had persistent bacteremia, which was higher than in patients with MIC $\leq 2\,\mu g/mL$ (1 of 7 patients, 14.3%) (not statistically significant; $p=0.088$). Thirty-day recurrence of bacteremia was evaluated in a total of 5 patients (26.3%), and 1 of 4 patients (25%) with MIC $\leq 2\,\mu g/mL$ and the 1 patient (100%) with MIC $>2\,\mu g/mL$ had recurrence of bacteremia (not statistically significant; $p=0.4$).

Next, we performed univariate analyses on the potential factors of TEIC treatment failure (Table 3). There were no significant differences between treatment success and failure groups in the main characteristics including age, gender, body weight, BMI, creatinine clearance, percentage of patients receiving hemodialysis, ICU admission at the onset of bacteremia, surgery within the previous 30 d, and comorbidities. The median SOFA scores were 3 (range, 0–6) and 6.5 (range, 0–11) in ''Success'' and ''Failure'' groups, respectively (not statistically significant; $p=0.107$). In the ''Success'' group, the source of bacteremia was catheter-related (3/11, 27.3%), respiratory tract (3/11, 27.3%), or skin/wound (3/11, 27.3%) infections. In the ''treatment failure'' group, patients had catheter-related (1/8, 12.5%), respiratory tract (4/8, 50%), or skin/wound (1/8, 12.5%) infections. The median of the initial TEIC trough level in the ''Success'' and ''Failure'' groups was 15.5 $\mu g/mL$ (range, 6.92–23.7 $\mu g/mL$) and 19.2 $\mu g/mL$ (range, 7.45–27.0 $\mu g/mL$), respectively (not statistically significant; $p=0.52$). Patients who had TEIC MIC $>2\,\mu g/mL$ in the ''Success'' and ''Failure'' groups were 0/11 (0%) and 4/8 (50%), respectively, and TEIC MIC $>2\,\mu g/mL$ was significantly associated with treatment failure [odds ratio, 23.0; 95% confidence interval (CI), 1.02–520.4].

Table 4 summarizes the patients' treatment outcomes and TEIC trough levels, including whether the case of death was due to infection.

DISCUSSION

We investigated the potential correlation between TEIC MIC and treatment outcomes in MRSA bacteremia. Several studies have shown the relationships between TEIC trough levels and clinical outcomes.[12,22–27] In our institution, current target trough levels of TEIC in the steady state is from 15 to 30 $\mu g/mL$, in accordance with Japanese therapeutic drug monitoring (TDM) guidelines from 2016.[31]

Table 3. Univariate Analysis of Potential Risk Factors of Treatment Failure

Variable	Success ($n=11$)	Failure ($n=8$)	Odds ratio (95% CI)	p value
Age, years	68 (23–84)	57 (26–77)		0.741
Gender, male	7 (63.6)	3 (37.5)	0.34 (0.05–2.26)	0.37
Body weight (kg)	61.3 (35.6–64)	55.3 (41.7–59.7)		0.536
BMI (kg/m^2)	20 (15.4–30.8)	21 (15.8–27)		0.625
Creatinine clearance (mL/min)	60.3 (19.3–174.3)	56.4 (13.9–136.4)		0.967
Hemodialysis	1 (9.1)	1 (12.5)	1.43 (0.08–26.91)	1
ICU at the onset of bacteremia	1 (9.1)	1 (12.5)	4.6 (0.16–128.6)	1
Surgery (within 30 d)	5 (45.5)	2 (25)	0.4 (0.05–2.94)	0.633
SOFA score	3 (0–6)	6.5 (0–11)		0.107
Comorbidity				
Diabetes mellitus	2 (18.2)	2 (25)	1.5 (0.16–13.76)	1
Cardiovascular disease	6 (54.6)	4 (50)	0.83 (0.13–5.17)	1
Stroke	2 (18.2)	2 (25)	1.5 (0.16–13.76)	1
Renal failure (creatinine >1.5 mg/dL)	4 (36.4)	2 (25)	0.58 (0.08–4.39)	1
Liver cirrhosis	0 (0)	0 (0)		
COPD	0 (0)	0 (0)		
Solid tumor	3 (27.3)	3 (37.5)	1.6 (0.23–11.27)	1
Hematological malignancy	4 (36.4)	6 (75)	5.25 (0.70–39.50)	0.17
Chemotherapy within 30 d	1 (9.1)	2 (25)	3.33 (0.25–45.14)	0.546
Neutropenia (ANC <500 mm^3)	0 (0)	1 (12.5)	4.6 (0.16–128.6)	0.421
Infective endocarditis	0 (0)	0 (0)		
Sepsis	5 (45.5)	4 (50)	1.2 (0.19–7.44)	1
Transplantation (solid)	0 (0)	0 (0)		
HIV	0 (0)	0 (0)		
Sources of infection				
Catheter-related	3 (27.3)	1 (12.5)	0.38 (0.03–4.55)	0.603
Respiratory tract	3 (27.3)	4 (50)	2.67 (0.39–18.17)	0.377
Skin/wound	3 (27.3)	1 (12.5)	0.38 (0.03–4.55)	0.603
Endocarditis	0 (0)	0 (0)		
Bone and joint	0 (0)	0 (0)		
Intra-abdominal	0 (0)	0 (0)		
Urinary tract	0 (0)	0 (0)		
Other site	0 (0)	1 (12.5)	4.6 (0.16–128.6)	0.421
Unknown primary site	2 (18.2)	1 (12.5)	0.64 (0.05–8.62)	1
TEIC trough level in plasma (μg/mL)[a]	15.5 (6.92–23.7)	19.2 (7.45–27.0)		0.52
TEIC MIC >2 (μg/mL)	0 (0)	4 (50)	23 (1.02–520.4)	0.018

[a] TEIC trough levels ($n=6$ for success and $n=6$ for failure) were compared. Data are presented as number (%) or median (range). p values were determined using Mann-Whitney U test for continuous data or Fisher's exact test for categorical data. Abbreviations: ANC, absolute neutrophil count; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; MIC, minimum inhibitory concentration; SOFA, Sequential Organ Failure Assessment; TEIC, teicoplanin.

During the investigation period of our study (2008 to 2014), the target TEIC steady-state trough levels were from 15 to 25 μg/mL, based on the 2013 TDM guidelines.[32] Although some patients exhibited insufficient initial TEIC trough levels (<10 μg/mL) in the MIC >2 μg/mL group, it is notable that patient number 19 with TEIC MIC >2 μg/mL and with persistent bacteremia died of MRSA sepsis within 60 d, although the patient's TEIC trough level was high enough (27.0 μg/mL) (Table 4). These results support the idea that high TEIC MICs lead to poor treatment outcomes even if the patients' TEIC trough level is near the upper limit of the recommended range.

Recently, several studies have demonstrated that a VCM MIC of 2 μg/mL is associated with VCM treatment failure, resulting in high mortality, compared to an MIC of 1 μg/mL, even though the CLSI guidelines shows that VCM MIC ≤ 2 μg/mL is considered as ''susceptible''.[1-4,15] Considering this fact, clinical efficacy may not necessarily correspond to the CLSI

Table 4. Summary of Patient Treatment Outcomes and TEIC Trough Levels

Patient No.	TEIC MIC (μg/mL)	Treatment outcome[a]	Death within 60 d from the onset of bacteremia		Persistent bacteremia	Duration of TEIC treatment (d)	TEIC trough level[b]	History of Anti-MRSA drug treatment[d] (duration, d)	Concomitant Antimicrobial agent(s)[e]	Detection of bacteria other than MRSA	SOFA score	Sources of infection
			Yes/No	Infection-related death (Yes/No)			(μg/mL) (Day[c])					
1	MIC ≤2	≤2	failure	yes	yes	disappeared	8	22.2 (4)	linezolid (7)	cefepime	*P. aeruginosa*	3	respiratory tract
2		≤2	success	no	—	n.d.	4	—	—	meropenem	*K. oxytoca*	6	skin/wound
3		≤2	success	no	—	disappeared	14	23.7 (5)	—	—	—	0	unknown primary site
4		≤2	failure	no	—	persistent	21	21.7 (7)	arbekacin (13)	doripenem	*P. aeruginosa* *S. maltophilia*	7	respiratory tract
5		≤2	success	no	—	disappeared	6	12.6 (4)	—	sulbactam/cefoperazone	—	3	respiratory tract
6		≤2	success	no	—	n.d.	6	—	—	meropenem	—	4	catheter-related
7		≤2	success	no	—	n.d.	6	6.92 (6)	vancomycin (20)	—	—	3	skin/wound
8		≤2	success	no	—	disappeared	52	13.8 (5)	vancomycin (2)	—	*P. aeruginosa*	3	respiratory tract
9		≤2	success	no	—	n.d.	19	—	teicoplanin (39)	—	—	4	unknown primary site
10		≤2	failure	no	—	disappeared	9	—	—	tazobactam/piperacillin	—	3	skin/wound
11		≤2	success	no	—	n.d.	14	20.0 (6)	—	minocycline ceftriaxone	—	1	catheter-related
12		≤2	success	no	—	disappeared	25	—	—	minocycline ciprofloxacin, ST	*A. xylosoxidans* *P. aeruginosa*	3	skin/wound
13		≤2	failure	yes	no	n.d.	13	16.8 (5)	arbekacin (2)	meropenem	*E. faecalis*	0	catheter-related
14		≤2	success	no	—	n.d.	14	15.5 (4)	—	tazobactam/piperacillin	—	6	catheter-related
15		≤2	success	no	—	n.d.	21	18.2 (4)	—	meropenem cefepime	—	3	respiratory tract
16	MIC >2	4	failure	yes	no	disappeared	9	—	teicoplanin (7)	meropenem	—	11	unknown primary site
17		4	failure	yes	yes	persistent	26	13.4 (16)	vancomycin (27)	gentamicin meropenem	*S. marcescens*	10	respiratory tract
18		8	failure	yes	yes	persistent	8	7.45 (6)	—	meropenem	*A.* species *E. faecalis*	11	other site
19		8	failure	yes	yes	persistent	17	27.0 (5)	—	sulbactam/cefoperazone	*P. aeruginosa*	6	respiratory tract

[a] TEIC treatment failure, the primary end point, was defined as a composite of all-cause 60-day mortality, persistent bacteremia, and/or 30-day recurrence of MRSA bacteremia. [b] Initial trough levels, which were excluded during hemodialysis. [c] The day of treatment when TEIC trough level was determined. [d] History of anti-MRSA drug therapy within 30 d prior to TEIC treatment. [e] Treatment with at least one dose of a concomitant antimicrobial agent(s) during the period of TEIC treatment. Abbreviations: *A.* species, *Acinetobacter* species; *A. xylosoxidans*, *Achromobacter xylosoxidans*; *E. faecalis*, *Enterococcus faecalis*; *K. oxytoca*, *Klebsiella oxytoca*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; n.d., not determined; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. maltophilia*, *Stenotrophomonas maltophilia*; *S. marcescens*, *Serratia marcescens*; SOFA, Sequential Organ Failure Assessment; TEIC, teicoplanin.

susceptibility breakpoint, especially when the MIC is close to the upper extremes of the CLSI susceptibility range. This is probably because the susceptibility test results were derived from *in vitro* studies.[15] While the relationship between high VCM MICs and VCM treatment failure have been reported in various studies,[1–4] there is little understanding on the association between TEIC MICs and their outcome.

We cannot completely exclude the possibility that the severity of underlying disease in the patient with MIC $>2\,\mu g/mL$ may have been different from the patient with MIC $\leq 2\,\mu g/mL$. As shown in Table 1, the SOFA score in patients with MIC $>2\,\mu g/mL$ was significantly higher than that in patients with MIC $\leq 2\,\mu g/mL$. However, there were no significant differences in this score between the ''success'' and ''failure'' groups (Table 3). On the contrary, the frequency of TEIC MIC $>2\,\mu g/mL$ was significantly higher in ''failure group'' than in ''success group'', suggesting that the risk factor for treatment failure was probably attributed to ''high'' MIC ($>2\,\mu g/mL$).

The limitations of this study were as follows; Firstly, enrolled number of patients was low. Therefore, we did not conduct multivariable analysis to exclude confounding factors such as severity score. In the present study, in order to rule out the influences of any other anti-MRSA antibiotics on the outcome of bacteremia, we excluded patients who received any other anti-MRSA antibiotics for >48 h before TEIC treatment. Thus, the number of patients enrolled in our study was low. Another limitation was the difference in SOFA score between the two groups (MIC $\leq$ 2 and MIC $>2\,\mu g/mL$) as shown in Table 1. SOFA score might probably be a major confounding factor because the high MIC group showed significantly higher SOFA score. However, we also reported that there was no significant difference between the treatment success and failure groups, as shown in Table 3. Thus, the high MIC group potentially included high SOFA score patients. This fact seemed to have been taken into consideration to precisely evaluate the treatment outcome of TEIC in treating the bacteremia.

As mentioned above, in the present study, the SOFA scores of patients with MIC $>2\,\mu g/mL$ were higher than those of patients with MIC $\leq 2\,\mu g/mL$ (Table 4). In addition, bacteria other than MRSA, such as *Pseudomonas aeruginosa*, were detected in cultures of blood and/or sources of infection from the patients. Thus, it is unclear whether patients with MIC $>2\,\mu g/mL$ died because of TEIC treatment failure, their worse general conditions, or other pathogen-induced infections.

As shown in Table 4, all four patients with MIC $>$ $2\,\mu g/mL$ (patient numbers 16–19) died within 60 d from the onset of bacteremia, of which three patients exhibited persistent bacteremia and MRSA sepsis (patient numbers 17–19). The details of their blood culture results are as follows: In the case of patient number 17, MRSA was repeatedly detected in cultures of blood during TEIC treatment. *Serratia marcescens* was also detected in blood culture, although it was only once. It remains unclear whether *S. marcescens* was associated with the poor outcome of this patient. However, because MRSA remained present, treatment failure of TEIC is considered to have at least been involved in the patients' outcome.

In the case of patient number 18, positive blood cultures for MRSA were repeatedly detected over 2 weeks despite TEIC treatment. Although *Acinetobacter* species and *Enterococcus faecalis* were also detected in blood culture, they disappeared after treatment with TEIC and meropenem. Therefore, the possibility that treatment failure occurred because of one or more pathogens other than MRSA was excluded. One of the causes of the poor treatment outcome seems to have been insufficient treatment intensity of TEIC; the patient's trough plasma level of TEIC was determined to be no more than $7.45\,\mu g/mL$ (at day 6 from the initiation of TEIC treatment), which is below the recommended therapeutic range.

In the case of patient number 19, blood cultures were positive for MRSA, and MRSA continued to be detected despite TEIC treatment with a high TEIC trough level ($27.0\,\mu g/mL$). Two weeks after the onset of MRSA bacteremia, MRSA and *P. aeruginosa* were also detected in a sputum culture, although this occurred only once. It remains unclear whether *P. aeruginosa* was associated with the outcome of this patient, but treatment failure of TEIC for MRSA seems to have at least been involved in the outcome because MRSA did not disappear during TEIC treatment.

For patient number 16, TEIC seemed to be effective because blood cultures ceased to be positive for MRSA after TEIC treatment. Pathogens other than MRSA were not observed in blood cultures from this

patient. The patient died due to an underlying disease unrelated to MRSA infection.

Among the 15 patients with MIC $\leq 2\,\mu g/mL$, two patients died within 60 d of the onset of bacteremia (patient numbers 1 and 13 in Table 4). In patient number 1, MRSA was detected in both blood and sputum cultures. However, the pathogen was eradicated from the blood and bacteremia was improved 1 week after treatment with TEIC (repeated sputum culture data were not obtained). *P. aeruginosa* was also detected in sputum culture. However, no sequential culture from sputum was performed after treatment with cefepime. This patient died 2 months after the onset of persisting pneumonia, which seems to have been caused by one or more pathogens other than MRSA; since MRSA was no longer detected in a blood culture after TEIC treatment. In the case of patient number 13, positive blood cultures for MRSA and *E. faecalis* were detected. Because blood culture data are not available for the period after treatment with TEIC, it remains unclear whether TEIC treatment eliminated these bacteria. However, in this patient, fever declined after the treatment, and TEIC was therefore considered to be effective for the bacteremia, although it is not possible to exclude the possibility that the decline in fever might have resulted from the immediate removal of the patient's catheter, which was the source of infection. After resolution of infection, this patient was transferred to another hospital, and died because of the underlying disease.

The 4 patients with MIC $>2\,\mu g/mL$ had been hospitalized in 2 wards. Patient numbers 17 and 18 had been hospitalized in the same ward. However, they occupied different rooms of the ward and their hospitalization periods differed by 2 years. Patient numbers 16 and 19 had also been hospitalized in different rooms of a single ward, and the periods when MRSA was detected in the blood cultures of these patients were 6 months apart. These facts indicate that the cases of the 4 patients with MIC $>2\,\mu g/mL$ were unrelated to nosocomial spread of specific TEIC-resistant strains among hospitalized patients sharing the same room.

Chang *et al*. investigated the influence of high TEIC MIC on clinical outcomes against MRSA bacteremia, where they studied clinical results and mortality between low MIC ($\leq 1.5\,\mu g/mL$) and high MIC ($>1.5\,\mu g/mL$).[21] They suggested that TEIC MIC $>1.5\,\mu g/mL$ was associated with poor outcome and bloodstream infection-related mortality. However, there was no difference in the 30-day mortality from the onset of bacteremia between the low and high MIC groups in their study.[21] On the contrary, in the present study, we investigated treatment outcomes of TEIC-administered patients in MRSA bacteremia comparing differences between TEIC MICs $\leq 2\,\mu g/mL$ and $>2\,\mu g/mL$, not $\leq 1.5\,\mu g/mL$ and $>1.5\,\mu g/mL$, because EUCAST suggested that the susceptibility breakpoint of TEIC is $2\,\mu g/mL$.[17] As a result, all 4 patients with TEIC MIC $>2\,\mu g/mL$ died within 60 d of the onset of bacteremia, of whom 3 died within 30 d.

In conclusion, our results suggest that TEIC treatment for MRSA bacteremia with TEIC MIC $>2\,\mu g/mL$ might be related to poor treatment outcomes, even though the CLSI-designated susceptibility range for TEIC MIC is $\leq 8\,\mu g/mL$. Consequently, when treating a patient with MRSA bacteremia and TEIC MIC $>2\,\mu g/mL$, it is recommended that alternative anti-MRSA agents should be considered.

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Conflict of Interest There are no conflicts of interest to declare.

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