ORIGINAL RESEARCH

Daptomycin versus teicoplanin for bloodstream infection due to methicillin-resistant *Staphylococcus aureus* with a high teicoplanin minimal inhibitory concentration ≥1.5 mg/L: a propensity score-based analysis

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Background: Recent reports have described decreased effectiveness of teicoplanin in the treatment of bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA) with teicoplanin minimal inhibitory concentration (MIC) ≥1.5 mg/L. Consensus guidelines recommend considering use of alternative agents for MRSA infections involving a higher teicoplanin MIC, despite of limited data to support this recommendation.

Patients and methods: To compare the clinical outcome among patients with bacteremia due to MRSA with teicoplanin MIC ≥1.5 mg/L, we included patients who received high-dose daptomycin (≥8 mg/kg/day) and those who received standard-dose (6 mg/kg/day) or high-dose (6 mg/kg/12 hours) maintenance teicoplanin. The primary endpoint was a favorable outcome, defined as the resolution of clinical signs and symptoms and a negative culture report at the end of therapy. Adjusted analyses were performed by multivariate analysis and propensity score-based matching.

Results: Of 142 patients eligible for inclusion, 28 (19.7%) were treated with high-dose daptomycin, 27 (19.0%) with high-dose teicoplanin, and 87 (61.3%) with standard-dose teicoplanin. In multivariate regression analysis, Pittsburgh bacteremia score ≥4 (OR, 5.3; 95%CI, 1.9–14.5) was independently associated with an unfavorable outcome. After propensity-score matching with age and Pittsburgh bacteremia score ≥4, patients on high-dose daptomycin were more likely to have favorable outcomes than those on standard-dose teicoplanin (74.1% vs 42.6%; *P*=0.02). However, there was no significant difference in terms of favorable outcomes (*P*=0.12) between patients receiving high-dose daptomycin and those receiving high-dose teicoplanin after the same propensity-score matching.

Conclusion: Treatment with high-dose daptomycin resulted in significantly better outcomes than with standard-dose teicoplanin in the treatment of MRSA bacteremia with teicoplanin MIC ≥1.5 mg/L. However, the clinical outcome of the patients receiving high-dose teicoplanin was similar to that of the patients receiving high-dose daptomycin.

Keywords: gram-positive bacteria, antimicrobial susceptibility, pharmacodynamics, glycopeptide, lipopeptide

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important etiology of severe infectious syndromes in the community and hospital.[1] MRSA bloodstream infection

(BSI) has been found to be associated with a higher risk of mortality, prolonged hospital stays, and high costs than BSI due to other pathogens.[2,3] Teicoplanin, a glycopeptide, is one of the treatment options for MRSA infection. It was widely reported to be efficient with fewer adverse effects when comparable with vancomycin for MRSA infection.[4] One retrospective study found out that the minimal inhibitory concentrations (MICs) ≥1.5 mg/L of teicoplanin was associated with an unfavorable outcome in patients receiving teicoplanin for MRSA bacteremia.[5] The question remains as to whether the poorer outcomes with higher teicoplanin MIC are due to ineffective treatment or other microbiological characteristics of the organism. Daptomycin, a lipopeptide class antibiotic that disrupts cell membrane function via calcium-dependent binding, has bactericidal activity in a concentration-dependent fashion,[6] and differs from the glycopeptides in that it exerts high bactericidal activity against both methicillin-susceptible and methicillin-resistant *Staphylococcus* strains.[1] Several treatment guidelines include high-dose daptomycin (8–10 mg/kg/day) as a therapeutic option for difficult-to-treat infections.[6–8] Furthermore, Kullar et al revealed that high-dose daptomycin, defined as ≥8 mg/kg/day, was an effective and safe antimicrobial in patients with infective endocarditis.[9] As a result, Infectious Diseases Society of America (IDSA) guidelines for the treatment of MRSA BSI recommend consideration of high-dose daptomycin in patients with persistent MRSA bacteremia after vancomycin failure.[6]

According to IDSA guidelines, for isolates with vancomycin MIC >1 mg/L (susceptible according to Clinical and Laboratory Standards Institute [CLSI] breakpoints),[10] an alternative to vancomycin should be used.[6] An earlier study of the factors associated with clinical failure in patients with MRSA bacteremia demonstrated the relationship between vancomycin MIC and clinical treatment failure in univariate analysis.[11] A multicenter prospective study of MRSA bacteremia reported that the success rate of treatment with vancomycin was 55.6% with vancomycin MICs ≤0.5 mg/L, whereas it was only 9.5% in cases with MICs of 1–2 mg/L.[12] These results were mainly supported by the premise that there is presumably less likelihood of achieving target vancomycin pharmacodynamic parameters with higher vancomycin MIC.

Recently, clinical data supporting that daptomycin was associated with a better outcome compared with vancomycin in the treatment of BSIs due to MRSA with higher vancomycin MICs are emerging.[13,14] Our previous data highlighted the importance of high-dose teicoplanin (6 mg/kg/12 hours) maintenance treatment, especially for severe

MRSA infections.[15] We also found that high-dose teicoplanin maintenance treatment was associated with more favorable outcomes than standard-dose teicoplanin (6 mg/kg/day) maintenance treatment in patients with MRSA bacteremia, regardless of the teicoplanin MIC.[16] Therefore, the question of whether daptomycin, rather than high-dose maintenance teicoplanin therapy, confers any benefit in cases of MRSA BSI with high teicoplanin MIC remains unanswered.

Randomized clinical trials of daptomycin vs teicoplanin for MRSA BSI due to strains with high teicoplanin MIC are lacking and the findings of previous reports are limited because of differences in the severity of bacteremia and demographics between patients receiving teicoplanin therapy and those receiving daptomycin therapy. In this propensity-score matched, retrospective study, we aimed to evaluate the effectiveness of standard-dose and high-dose teicoplanin vs daptomycin in the treatment of bacteremia due to MRSA isolates with high teicoplanin MIC (≥1.5 mg/L) but still within the range of susceptibility designed by EUCAST (≤2 mg/L).

Patients and methods
Study design

Patients with MRSA BSI, who were admitted to a 2,700-bed tertiary care hospital in southern Taiwan over a 6-year period (2012–2017), were eligible for inclusion. Furthermore, patients were eligible if they 1) had an index MRSA bloodstream isolate with teicoplanin MIC of 1.5 or 2 mg/L, as determined by Etest® (bio-Merieux™, Marcy l'Etoile, France); 2) received either teicoplanin or daptomycin within 48 hours of the onset of infection; 3) received treatment with teicoplanin or daptomycin for >72 hours; and 4) were aged ≥18 years. If the patients experienced more than one episode of MRSA bacteremia, only the first episode was included. Patients with a concurrent infection by microbe(s) other than MRSA or those receiving adjunctive antibiotics for MRSA bacteremia were excluded from the study. Through the antimicrobial stewardship program in the hospital,[17] teicoplanin or daptomycin was prescribed at the discretion of the attending physician and all these prescriptions were approved by specialists of infectious diseases. Clinical data were retrieved from the medical records using a standardized case report form.

Adequate teicoplanin therapy was defined as a loading dose of 6 mg/kg administered thrice 12 hours apart,[18] followed by a maintenance dose of 6 mg/kg/12 hours (high-dose teicoplanin group) or 6 mg/kg/24 hours (standard-dose teicoplanin group) or the adjusted equivalent doses for patients with impaired renal function according to the package insert

(Sanofi-Aventis™, Paris, France). The dose of daptomycin was ≥8 mg/kg/24 hours (high-dose daptomycin group) or the adjusted equivalents for renal insufficiency. The patients were made anonymous to maintain confidentiality of the data. The Institutional Review Board of the CGMH approved the study (No. 201601482B0) and waived the need for patient consent because of the retrospective nature of the study.

Microbiological methods

MRSA was defined as an isolate of *S. aureus* subjected to susceptibility testing using the disk diffusion method, in which cefoxitin (30 µg) produced an inhibition zone of ≤21 mm according to CLSI recommendation.[10] The MICs of teicoplanin and daptomycin were determined using Etest teicoplanin and daptomycin strips (AB Biodisk™, Solna, Sweden), separately.

Definitions

The severity of the underlying medical illness was stratified according to the McCabe score and categorized as rapidly fatal, ultimately fatal, or nonfatal.[19] The clinical severity of the illness at the time of sampling blood for cultures was stratified using the modified Pittsburgh bacteremia score, and critical illness was defined as Pittsburgh bacteremia score ≥4 points.[20] Sources of bacteremia were identified according to the clinical, microbiologic, imaging findings, and the judgment of the physicians. Bacteremia in a patient with no apparent focus of infection other than blood was defined as bacteremia with no identified focus of infection. Catheter-related bacteremia was defined if the inserted catheter had been in place for more than 72 hours and culture of the clipped distant 5-cm tip of the removed catheter by rolling it on a culture medium yielded more than 15 colonies of MRSA; or the culture of purulent discharge from the catheter exit grew MRSA.[21] Bone and joint infection was defined based on clinical manifestations with consistent histopathological and/or radiographical findings.[22] Infective endocarditis was defined as histopathology was found in the valvular specimens obtained during surgery, or valvular vegetations were sonographically revealed regardless of an embolic phenomenon.[23] Soft tissue infection was considered when MRSA grew from the specimen sampled from the affected site.[22] Intra-abdominal infection was defined as the infection that extended into the peritoneal space was associated with abscess formation or peritonitis, and growth of MRSA on cultures of the peritoneal fluid, bile, or intra-abdominal abscess.[24] Urinary tract infection was considered when MRSA, as the only identified pathogen, grew more than 10^5 colony-forming units per milliliter in the urine culture.[22]

Pneumonia referred to the presence of clinical symptoms/signs of lower respiratory tract infection, accompanied with consistent radiographic findings.[22] Adequate source control was defined as timely 1) percutaneous or surgical intervention to drain the collection(s) of infected fluid, debride the infected tissues, and control ongoing enteric or other drainage-producing intra-abdominal source of infection; 2) removal of central venous catheter for catheter-related bacteremia; and 3) removal of urinary catheter for BSI secondary to catheter-related urinary tract infection. Subjects were classified into three groups at the time of the switch to daptomycin: no improvement during current therapy, adverse event due to current therapy, or undetermined reason.

Early clinical response was assessed on day 7 after initiating anti-MRSA therapy, while the evaluation upon completion of teicoplanin or daptomycin therapy was referred as the final clinical response. Patients were evaluated on day 7 for the presence of septic shock, persistent bacteremia, persistent fever, or persistent leukocytosis, and favorable and unfavorable early clinical responses referred to the absence and presence of any of these findings, respectively.[6] The primary endpoint was a favorable outcome, which was defined as the resolution of clinical signs and symptoms and a negative culture report at the end of therapy. Clinical progression or relapse of sepsis that had previously improved clinically, mortality, and/or culture of blood sampled at the end of daptomycin or teicoplanin treatment that remained positive for MRSA were defined as "unfavorable" outcomes. Additionally, 30-day overall mortality was defined as all causes of mortality occurring within 30 days of hospitalization after the onset of MRSA BSI.

Statistical analysis

In univariate analysis, Student's *t*-test or Mann–Whitney *U*-test was used for comparisons between continuous variables, whereas the chi-squared test or Fisher's exact test was used for comparisons between dichotomous variables. Variables with a *P*-value <0.1 in univariate analyses were incorporated into a stepwise, backward logistic regression model to determine independent variables associated with favorable outcomes at the end of the initial teicoplanin or daptomycin treatment. Hosmer–Lemeshow goodness-of-fit tests were performed to evaluate the predictive performance of the logistic regression model. The propensity score was calculated using independent predictors of favorable outcomes at the end of initial teicoplanin or daptomycin treatment, which were assessed using a multivariable logistic regression model. The patients who received high-dose daptomycin

were matched on a 1:1 and 1:2 basis with those treated with high-dose teicoplanin and standard-dose teicoplanin patients, respectively, and the matching by the closest total scores was performed manually based on a tolerance interval approach. As described previously,[25] matching tolerance is a propensity score difference of 0.2: a patient in the high-dose daptomycin treatment group was matched with a patient in the high-dose teicoplanin or standard-dose teicoplanin group only when the estimated probability of the high-dose daptomycin group was within 20% of the estimated probability of his or her counterpart who was treated with high-dose teicoplanin or standard-dose teicoplanin. Statistical analyses were performed using SPSS® version 21 (IMB Inc.™, Armonk, NY, USA). All tests were two tailed and variables with a *P*-value <0.05 were regarded as statistically significant.

Results

A total of 184 adult patients with MRSA BSI with high teicoplanin MIC (≥1.5 mg/L) were identified over the study period, of which 42 who received nonadequate dosage or treatment more than 48 hours after the onset of infection with teicoplanin, daptomycin, and other treatments except teicoplanin or daptomycin for MRSA bacteremia were excluded (Figure 1). Of the 142 patients included, 28 (19.7%) were treated with high-dose daptomycin, 27 (19.0%) with high-dose teicoplanin, and 87 (61.3%) with standard-dose teicoplanin. The rate of adequate control of the source of infection in patients on standard-dose teicoplanin, high-dose teicoplanin, and high-dose daptomycin was 77.2%, 84.2%, and 76.2%, respectively. The rate of favorable outcome at the end of the initial therapy was 29.9% in the standard-dose teicoplanin group, 62.9% in the high-dose teicoplanin group, and 71.4% in the high-dose daptomycin group (Figure 1). Of the 87 patients who received initial standard-dose teicoplanin, 32 (36.8%) received sequential therapy with high-dose daptomycin. The median time to switching from teicoplanin to daptomycin was 6 days (interquartile range, 4–10 days). The reason for switching was clinical failure in 24 patients (75.0%), physician reference in 4 (12.5%), adverse events in 2 (6.3%), and unspecified reasons in 2 (6.3%). The 30-day overall mortality rate in patients on continuous standard-dose teicoplanin and that in those who were subsequently switched to daptomycin treatment was 36.6% and 21.9%, respectively (*P*=0.21, Fisher's exact test). No patient in the high-dose
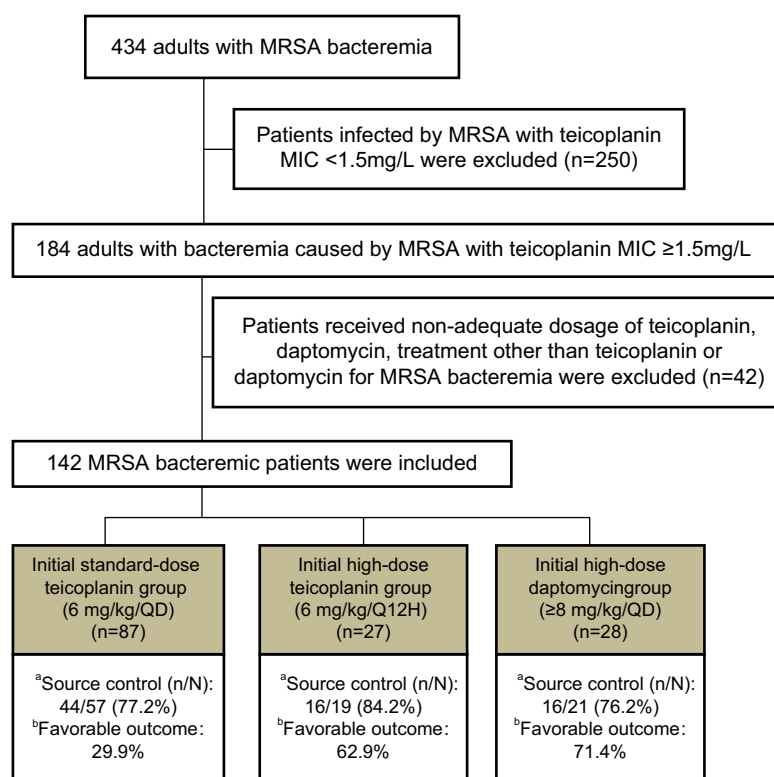
Figure 1 Flowchart of the study.
Notes: [a]Surgical intervention, drainage, central venous catheter removal, and urinary catheter removal were defined as source control. Patients with pneumonia or primary bacteremia were excluded. n: adequate and timely removal or debridement of the source of bacteremia, N: source of bacteremia needed to be removed or debrided. [b]Evaluation at the completion of initial teicoplanin or daptomycin therapy.

teicoplanin or high-dose daptomycin group needed to switch to daptomycin or teicoplanin, respectively.

Univariate analyses were used to compare the groups with favorable outcomes and those with unfavorable outcomes at the end of the initial teicoplanin or daptomycin treatment. The variables for comparison were clinical characteristics, demographics, source of bacteremia, major comorbidities, severities of the comorbidities, BSI severity at onset, adequate infection control, and initial treatment group (Table 1). We found that critical illness (Pittsburgh bacteremia score ≥4) at BSI onset and initial treatment with standard-dose teicoplanin were negatively associated with outcomes. Additionally, initial treatment with high-dose daptomycin was significantly positively associated with favorable outcomes. In subsequent multivariate regression analysis, Pittsburgh bacteremia score ≥4 (OR, 5.3; 95%CI, 1.9–14.5; P=0.01) was independently associated with unfavorable outcomes at the end of the initial teicoplanin or daptomycin treatment (Table 1). The P-values for the Hosmer–Lemeshow goodness-of-fit tests were >0.05. Hence, there is no significant evidence of lack of fit for any of the final models.

The patients in the standard-dose teicoplanin group and high-dose daptomycin group were matched in a ratio of 2:1 with the closest propensity scores on the basis of age and critical illness (Pittsburgh bacteremia score ≥4; Table 2). After propensity-score matching, patients in the high-dose daptomycin group had better short-term favorable outcomes (66.7% vs 38.9%; P=0.03) and favorable outcomes at end of therapy (74.1% vs 42.6%; P=0.02) compared with those in the standard-dose teicoplanin group. Patients in the high-dose

Table 1 Risk factors for favorable outcome at the end of initial teicoplanin or daptomycin treatment in 142 adult patients with MRSA bacteremia with teicoplanin MIC ≥1.5 mg/L

Outcome at the end of the initial treatment	Favorable outcome N=60 (%)	Unfavorable outcome N=82 (%)	P-value
Demographics			
Male gender, n (%)	39 (65.0)	45 (54.9)	0.30
Age, mean (range), years	67 (57–78)	72 (61–81)	0.20
Co-morbidities, n (%)			
Coronary artery disease	9 (15.0)	25 (30.5)	0.05
Diabetes mellitus	32 (53.3)	44 (53.7)	>0.99
Hypertension	28 (46.7)	46 (56.1)	0.31
Solid tumor	15 (25.0)	10 (12.2)	0.07
Liver cirrhosis	8 (13.3)	11 (13.4)	>0.99
COPD	7 (11.7)	13 (15.9)	0.63
End-stage renal disease	13 (21.7)	27 (32.9)	0.19
Cerebral vascular accident	19 (31.7)	30 (36.6)	0.60
Prosthetic device implantation	21 (35.0)	33 (40.2)	0.60
Pittsburgh bacteremia score ≥4[a]	9 (15.0)	48 (60.0)	<0.01[b]
Ultimately and rapid fatal comorbidity (McCabe classification)	21 (35.0)	33 (40.2)	0.60
Source of bacteremia,[c] n (%)			
Catheter-related bacteremia	11 (18.3)	18 (22.0)	0.68
Bone and joint infection	15 (25.0)	14 (17.1)	0.29
Infective endocarditis	1 (1.7)	6 (7.3)	0.24
Skin and soft infection	14 (23.3)	15 (18.3)	0.53
Intra-abdominal infection	3 (5.0)	2 (2.4)	0.65
Urinary tract infection	4 (6.7)	1 (1.2)	0.16
Pneumonia	4 (6.7)	13 (15.9)	0.12
Primary bacteremia	8 (13.3)	13 (15.9)	0.81
Adequate infection source control rate[d] n/N	38/44 (86.4)	40/55 (72.7)	0.14
Initial treatment group, n (%)			
Standard-dose teicoplanin (6 mg/kg/QD)	25 (41.7)	62 (75.6)	<0.01
High-dose teicoplanin (6 mg/kg/Q12H)	15 (25.0)	12 (14.6)	0.13
High-dose daptomycin	20 (33.3)	8 (9.8)	<0.01

Notes: [a]At the time of sampling blood for culture. [b]In multivariate analysis, Pittsburgh bacteremia score ≥4 (OR, 5.3; 95%CI, 1.9–14.5; P=0.01) was a risk factor for unfavorable outcome at the end of the initial teicoplanin or daptomycin treatment in patients with MRSA bacteremia with teicoplanin MIC ≥1.5 mg/L. [c]Patients might have had more than one source of bacteremia. [d]Surgical intervention, drainage, central venous catheter removal, and urinary catheter removal were defined as source control. Patients with pneumonia or primary bacteremia were excluded. n: adequate and timely removal or debridement of the source of bacteremia, N: source of bacteremia that needed to be removed or debrided.
Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2 Clinical characteristics, responses, and outcomes in adults with MRSA bacteremia with teicoplanin MIC ≥1.5 mg/L and treated with standard-dose teicoplanin or daptomycin

Variables	Initial standard-dose teicoplanin, N=87 (%)	Initial daptomycin, N=28 (%)	P-value	Initial standard-dose teicoplanin, N=54 (%)	Initial daptomycin, N=27 (%)	P-value[a]
Demographics						
Male gender, n (%)	51 (58.6)	15 (53.6)	0.67	30 (55.6)	15 (55.6)	>0.99
Age, mean (range), years	72 (61–81)	68 (58–78)	0.29	NA	NA	NA
Length of hospital stay, mean (range), days	33 (17–52)	31 (21–43)	0.99	34 (20–55)	32 (21–43)	0.75
Duration of initial antibiotics therapy, mean (range), days	7 (4–14)	14 (9–18)	<0.01	11 (5–15)	14 (10–16)	0.09
Comorbidities, n (%)						
Coronary artery disease	29 (33.3)	2 (7.1)	0.01	18 (33.3)	2 (7.4)	0.02
Diabetes mellitus	50 (57.5)	15 (53.6)	0.83	37 (68.5)	15 (55.6)	0.25
Hypertension	48 (55.2)	13 (48.1)	0.52	36 (66.7)	13 (48.1)	0.10
Solid tumor	12 (13.8)	6 (21.4)	0.37	6 (11.1)	5 (18.5)	0.40
Liver cirrhosis	12 (13.8)	4 (14.3)	>0.99	5 (9.3)	4 (14.8)	0.48
COPD	12 (13.8)	1 (3.6)	0.18	5 (9.3)	1 (3.7)	0.40
End-stage renal disease	33 (37.9)	7 (25.0)	0.26	19 (35.2)	7 (25.9)	0.35
Cerebral vascular accident	31 (35.6)	7 (25.0)	0.36	17 (31.5)	7 (25.9)	0.61
Prosthetic device implantation	34 (39.1)	13 (46.4)	0.51	19 (35.2)	12 (44.4)	0.41
Pittsburgh bacteremia score ≥4[b]	44 (50.6)	8 (28.6)	0.05	NA	NA	NA
Ultimately and rapid fatal comorbidity (McCabe classification), n (%)	34 (39.1)	13 (46.4)	0.51	21 (38.9)	12 (44.4)	0.64
Source of bacteremia,[c] n (%)						
Catheter-related bacteremia	22 (25.3)	2 (7.1)	0.06	12 (22.2)	2 (7.4)	0.15
Bone and joint infection	11 (12.6)	9 (32.1)	0.02	9 (16.7)	9 (33.3)	0.11
Infective endocarditis	4 (4.6)	2 (7.1)	0.63	2 (3.7)	2 (7.4)	0.49
Skin and soft infection	18 (20.7)	8 (28.6)	0.44	15 (27.8)	8 (29.6)	0.86
Intra-abdominal infection	2 (2.3)	2 (7.1)	0.25	2 (3.7)	1 (3.7)	>0.99
Urinary tract infection	2 (2.3)	1 (3.6)	0.57	1 (1.9)	1 (3.7)	0.62
Pneumonia	14 (16.1)	0	0.02	8 (14.8)	0	0.25
Primary bacteremia	14 (16.1)	4 (14.3)	>0.99	5 (9.3)	4 (14.8)	0.48
Adequate infection source control rate[d] n/N	44/57 (77.2)	16/21 (76.2)	>0.99	33/40 (82.5)	16/20 (80.0)	0.37
Clinical outcome, n (%)						
Short-term favorable outcome[e]	23 (26.4)	18 (64.3)	<0.01	21 (38.9)	18 (66.7)	0.03
Favorable outcome[f]	26 (29.9)	20 (71.4)	<0.01	23 (42.6)	20 (74.1)	0.02

Notes: [a]2:1 Match with propensity score (age and Pittsburgh bacteremia score ≥4). [b]At the time of sampling blood for culture. [c]Patients might have had more than one source of bacteremia. [d]Surgical intervention, drainage, central venous catheter removal, and urinary catheter removal were defined as source control. Patients with pneumonia or primary bacteremia were excluded. n: adequate and timely removal or debridement of the source of bacteremia, N: source of bacteremia needed to be removed or debrided. [e]Assessment on day 7 after starting the initial teicoplanin or daptomycin therapy. [f]Evaluation at the time of completion of the initial teicoplanin or daptomycin therapy.
Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

teicoplanin group and high-dose daptomycin group were matched in a ratio of 1:1 with the closest propensity scores on the basis of age and critical illness (Pittsburgh bacteremia score ≥4; Table 3). However, there was no significant difference in terms of favorable outcomes in the short term (P=0.37) and at the end of therapy (P=0.12) between these two groups.

The distribution of daptomycin MICs among the 28 patients in the high-dose daptomycin treatment group is shown in Table 4. A total of 21 (75.0%) patients were infected by MRSA strains with daptomycin MIC ≤0.25 mg/L. The favorable outcomes were found in patients who were infected

by MRSA strains with daptomycin MIC ≤0.25 mg/L than those who were infected by MRSA strains with daptomycin MIC >0.25 mg/L (81.9% vs 42.9%); however, the difference was not statistically significant (P=0.14, Table 4).

Discussion

Chang et al described that MRSA bacteremia with MIC of teicoplanin ≥1.5 mg/L was a predictor of unfavorable outcomes in patients receiving teicoplanin treatment.[5] In agreement with their findings,[5] our previous study observed a suboptimal clinical outcome when standard-dose teicoplanin was administered as a maintenance therapy for bacteremia caused

Table 3 Clinical characteristics, responses, and outcomes in adults with MRSA bacteremia with teicoplanin MIC ≥1.5 mg/L and treated with high-dose teicoplanin or daptomycin

Variables	Initial high-dose teicoplanin, N=27 (%)	Initial daptomycin, N=28 (%)	*P*-value	Initial high-dose teicoplanin, N=25 (%)	Initial daptomycin, N=25 (%)	*P*-value[a]
Demographics						
Male gender, n (%)	(66.6)	15 (53.6)	0.41	17 (68.0)	14 (56.0)	0.44
Age, mean (range), years	64 (55–78)	68 (58–78)	0.76	NA	NA	NA
Length of hospital stay, mean (range), days	43 (31–55)	31 (21–43)	0.13	41 (28–52)	35 (21–45)	0.74
Duration of initial antibiotics therapy, mean (range), days	13 (9–17)	14 (9–18)	0.51	13 (8–17)	14 (10–21)	0.13
Comorbidities, n (%)						
Coronary artery disease	3 (11.1)	2 (7.1)	0.67	3 (12.0)	2 (8.0)	0.57
Diabetes mellitus	11(40.7)	15 (53.6)	0.42	9 (36.0)	13 (52.0)	0.22
Hypertension	13 (48.1)	13 (48.1)	>0.99	12 (48.0)	11 (44.0)	0.74
Solid tumor	7 (25.9)	6 (21.4)	0.76	7 (28.0)	5 (20.0)	0.48
Liver cirrhosis	3 (11.1)	4 (14.3)	>0.99	3 (12.0)	4 (16.0)	0.71
COPD	7 (25.9)	1 (3.6)	0.03	6 (24.0)	0	0.21
End-stage renal disease	0	7 (25.0)	0.01	0	5 (20.0)	0.26
Cerebral vascular accident	11 (40.7)	7 (25.0)	0.26	10 (40.0)	7 (28.0)	0.33
Prosthetic device implantation	7 (25.9)	13 (46.4)	0.16	7 (28.0)	11 (44.0)	0.26
Pittsburgh bacteremia score ≥4[b]	5 (18.5)	8 (28.6)	0.53	NA	NA	NA
Ultimately and rapid fatal comorbidity (McCabe classification)	7 (25.9)	13 (46.4)	0.16	7 (28.0)	11 (44.0)	0.26
Source of bacteremia[c], n (%)						
Catheter-related bacteremia	5 (18.5)	2 (7.1)	0.25	5 (20.0)	2 (8.0)	0.27
Bone and joint infection	9 (33.3)	9 (32.1)	>0.99	8 (32.0)	8 (32.0)	>0.99
Infective endocarditis	1 (3.7)	2 (7.1)	>0.99	1 (4.0)	1 (4.0)	>0.99
Skin and soft infection	3 (11.1)	8 (28.6)	0.18	3 (12.0)	7 (28.0)	0.18
Intra-abdominal infection	1 (3.7)	2 (7.1)	>0.99	0	2 (8.0)	0.02
Urinary tract infection	2 (7.4)	1 (3.6)	0.61	2 (8.0)	1 (4.0)	0.57
Pneumonia	3 (11.1)	0	0.11	3 (12.0)	0	0.38
Primary bacteremia	3 (11.1)	4 (14.3)	>0.99	3 (12.0)	4 (16.0)	0.66
Adequate infection source control rate[d] n/N	16/19 (84.2)	16/21 (76.2)	0.70	15/17 (88.2)	15/18 (83.3)	0.57
Clinical outcome, n (%)						
Short-term favorable outcome[e]	16 (59.3)	18 (64.3)	0.79	14 (56.0)	17 (68.0)	0.37
Favorable outcome[f]	15 (55.6)	20 (71.4)	0.27	14 (56.0)	20 (80.0)	0.12

Notes: [a]1:1 Match with propensity score (age and Pittsburgh bacteremia score ≥4). [b]At the time of sampling blood for culture. [c]Patients might had more than one source of bacteremia. [d]Surgical intervention, drainage, central venous catheter removal, and urinary catheter removal were defined as source control. Patients with pneumonia or primary bacteremia were excluded. n: adequate and timely removal or debridement of the source of bacteremia, N: source of bacteremia needed to be removed or debrided. [e]Assessment on day 7 after starting the initial teicoplanin or daptomycin therapy. [f]Evaluation at the time of completion of the initial teicoplanin or daptomycin therapy.
Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

Table 4 The outcomes at the end of the initial daptomycin therapy at different distributions of daptomycin MIC

MIC of daptomycin (mg/L)	≤0.25 (N=21)	>0.25 (N=7)	*P*-value
Adequate infection source control rate[a] n/N (%)	12/14 (85.7)	4/7 (57.1)	0.28
Favorable outcome[b] n (%)	17 (81.9)	3 (42.9)	0.14

Notes: [a]Surgical intervention, drainage, central venous catheter removal, and urinary catheter removal were defined as source control. Patients with pneumonia or primary bacteremia were excluded. n: adequate and timely removal of central catheter, urinary catheter, or debridement of the source of bacteremia, N: source of bacteremia needed to be removed or debrided. [b]Evaluation at the time of completion of the initial daptomycin therapy.
Abbreviation: MIC, minimal inhibitory concentration.

by MRSA with teicoplanin MICs ≥1.5 mg/L.[16] Furthermore, patients on high-dose teicoplanin maintenance treatment had favorable outcomes in the case of MRSA bacteremia, regardless of the teicoplanin MIC values.[16] These findings highlighted that a higher dosage of this antibiotic was required to reach an appropriate pharmacokinetic target to optimize its activity against MRSA, if teicoplanin MICs were ≥1.5 mg/L. Additionally, several studies reported that daptomycin might

be used at higher doses for difficult-to-treat infections.[26,27] Therefore, in this study, we included adults with bacteremia due to MRSA strains with teicoplanin MICs ≥1.5 mg/L, who had received high/standard-dose maintenance teicoplanin or high-dose daptomycin for further evaluation.

To the best of our knowledge, the current study is the first study to compare the clinical outcomes in these patients. Moreover, propensity-score matching analyses are especially useful for retrospective observational studies, which might overcome the differences in the distribution of baseline covariates between treatment groups because they provide a natural weighing scheme that yields unbiased estimates of the impact of the treatment.[28] The current analyses controlled for the baseline factors linked to favorable outcomes at the end of initial teicoplanin or daptomycin therapy between patients in the high-dose teicoplanin, standard-dose teicoplanin, and high-dose daptomycin groups. Our results revealed that treatment with high-dose daptomycin resulted in significantly improved outcomes than did treatment with standard-dose teicoplanin (Table 2). However, the clinical outcome of the patients receiving high-dose teicoplanin was similar to that of the patients receiving high-dose daptomycin (Table 3). In this study, the therapy was changed to daptomycin in most patients of the standard-dose teicoplanin group because their clinical status was worsening or not improving on the current therapy. This delay in the initiation of daptomycin was not associated with better outcomes. The results suggest that switching the treatment from standard-dose teicoplanin to daptomycin, particularly late in the course of infection, may not lead to more favorable outcomes in comparison with the continuation of standard-dose teicoplanin. Additionally, Falcone et al reported that daptomycin treatment was associated with a reduction in the duration of antibiotic therapy in patients with MRSA BSI.[29] In their study, a higher percentage of patients in the glycopeptide group had a central venous catheter or other intravascular devices in place than did those of the daptomycin group.[29] The duration of antibiotic therapy was not shorter in our patients in the daptomycin group when compared with those in the high-dose teicoplanin group. It might be because of similar rates of adequate control of the source of infection between our patients in the high-dose teicoplanin and daptomycin treatment groups (Table 3).

Given that the bactericidal activity of glycopeptides is dependent on the concentration–time curve to MIC ratio (area under the curve [AUC_{24}/MIC]) and the peak concentration to MIC ratio, administering higher doses could have a positive impact on patient outcomes. According to previous

reports,[30,31] the average of teicoplanin C_{min} was 10 mg/L on day 6 in patients receiving teicoplanin maintenance doses of 6 mg/kg/24 hours, after loading doses of 6 mg/kg/12 hours. However, the teicoplanin C_{min} achieved to 10 mg/L on day 2 in patients whom teicoplanin maintenance doses of 6 mg/kg/12 hours were continued after loading doses of 6 mg/kg/12 hours.[30,31] The higher rate of clinical failure in the standard-dose regimen group might be related to the inability to achieve the AUC_{24}/MIC target when teicoplanin MIC exceeds 1 mg/L.[16] Daptomycin's rapid bactericidal and concentration-dependent activity may have contributed to the more favorable outcomes.[32] As a result, daptomycin was associated with significantly less clinical failure when compared with vancomycin or standard-dose teicoplanin in the setting of MRSA BSI with glycopeptides MICs ≥1.5 mg/L in recently published studies[13,14] as well as in the current cohort.

This study still had several limitations. First, despite retrieving patient outcomes based on favorable outcomes at the end of initial teicoplanin or daptomycin treatment to minimize the confounding of the primary endpoint, this retrospective approach for other parameters has inherent limitations because of potential confounding and selection bias. Multicenter, prospective, randomized trials are needed to validate our findings. Second, to adequately assess the treatment impact for MRSA BSI, several exclusion criteria were implemented, which might have limited its external validity. However, patients receiving inadequate dosage of teicoplanin or daptomycin were excluded from our population, which should have maximal effect on the clinical outcomes. Third, this is a retrospective study in a single institution that included a limited number of patients with bacteremia due to MRSA strains with teicoplanin MICs ≥1.5 mg/L; thus, its generalizability is limited. Fourth, molecular analyses were not performed to identify the specific MRSA strains and clones with teicoplanin MICs ≥1.5 mg/L that might be prevalent in the hospital during the study period. Finally, analyses of serum teicoplanin and daptomycin levels were not performed because no commercialized methods were available to determine these levels. Nevertheless, high teicoplanin maintenance dose regimens and daptomycin dose regimens greater than the FDA-approved dose of 6 mg/kg daily have been associated with safety and potentially more favorable outcomes in previous observational studies.[13,15,16]

Conclusions

In patients with bacteremia due to MRSA strains with teicoplanin MICs ≥1.5 mg/L, Pittsburgh bacteremia score ≥4 was

an independent risk factor for unfavorable outcomes. After propensity-score matching, patients in the high-dose daptomycin group had better short-term outcomes and outcomes at the end of therapy than did those in the standard-dose teicoplanin group. However, the clinical outcomes of the patients in the high-dose teicoplanin maintenance dose group were similar to those in the high-dose daptomycin group.

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Disclosure

The authors report no conflicts of interest in this work.

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