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Original article

Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose

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ABSTRACT

Treatment options for vancomycin-resistant enterococci (VRE) bloodstream infection are limited. Studies comparing daptomycin or linezolid in treating VRE bloodstream infection have conflicting results and suggest daptomycin underdosing. The responses to different daptomycin doses have not been studied. We conducted a multicentre prospective cohort study to compare linezolid and daptomycin (≥6 mg/kg) for the treatment of VRE bloodstream infection. The primary outcome was 14-day mortality. We used multivariate logistic regression analysis for outcome analysis and a generalized additive model for dose-dependent response estimation. Two hundred twelve patients were included (daptomycin, $n = 141$; linezolid, $n = 71$). All-cause 14-day mortality was higher in the daptomycin group (36.9% vs. 21.1%; p 0.03). After adjusting for confounders in logistic regression, mortality was lower in the linezolid group (adjusted odds ratio (aOR), 0.45; 95% confidence interval (CI), 0.21–0.96; p 0.04). The generalized additive model showed that higher-dose daptomycin (≥9 mg/kg) was associated with better survival than lower-dose daptomycin (6–9 mg/kg). Logistic regression showed that linezolid (aOR, 0.36; 95% CI, 0.17–0.79; p 0.01) and higher-dose daptomycin (aOR, 0.26; 95% CI, 0.09–0.74; p 0.01) independently predicted lower mortality compared to lower-dose daptomycin. Linezolid was not superior to higher-dose daptomycin in terms of mortality (aOR, 1.40; 95% CI, 0.45–4.37; p 0.57). Higher-dose daptomycin had lower mortality than lower-dose daptomycin. Despite higher mortality for lower-dose daptomycin than linezolid, linezolid conferred no survival benefit compared to higher-dose daptomycin. Our findings suggest that the recommended daptomycin dose is suboptimal for treating VRE bacteraemia. **Y.-C. Chuang, CMI 2016;22:890.e1–890.e7**

Introduction

Vancomycin-resistant enterococci (VRE) has emerged as an important pathogen causing nosocomial infections [1] after it was first described in 1986 [2,3]. Vancomycin resistance is an important predictor of mortality of enterococcal bacteraemia [4]. However, treatment options are limited [5]. Linezolid is approved for VRE infection [6]. However, because of its bacteriostatic nature, there are concerns about using linezolid for treating VRE bacteraemia [7].

Daptomycin has rapid bactericidal activity against enterococci [7]. Although the recent study by Britt *et al.* [8] showed that daptomycin is superior to linezolid in treating VRE bacteraemia, their results differed from those of other studies [9,10]. Several important limitations of previous studies should be noted [8,11–16]. All of the previous studies were retrospective and may have been affected by recall bias. In addition, the recommended daptomycin dose was 6 mg/kg [17] and was based on the treatment of *Staphylococcus aureus* bacteraemia. One case series demonstrated daptomycin-treated VRE bacteraemic patients receiving a daptomycin dose of

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>6 mg/kg had a better outcome than those receiving a lower dose [18]. The daptomycin dose has varied widely in previous studies [19]. Because daptomycin exhibits concentration-dependent bacterial killing, underdosing may lead to underestimation of the efficacy of daptomycin [19]. However, it is unclear whether the dose differences can explain the conflicting results. To our knowledge, the responses to different doses of daptomycin have not been studied in patients who received daptomycin at a dose ≥6 mg/kg.

The primary aim of this multicentre prospective cohort study was to examine whether daptomycin at a dose ≥6 mg/kg would be associated with a higher survival rate compared to linezolid. Our secondary aim was to analyse whether higher daptomycin dose would result in better survival outcomes.

Methods

Hospital setting and patients

The study was conducted at the National Taiwan University Hospital (NTUH), a 2200-bed medical centre located in Taipei City and NTUH Yun-Lin Branch, a 600-bed teaching hospital in Yun-Lin county. The study was approved by the research ethics committee of the NTUH (NTUH 201011023RB). The informed consent process was waived by the ethics committee.

We used a previously collected database originally designed to follow VRE bacteraemic patients. Patients with VRE bacteraemia were enrolled prospectively from January 2010 through July 2015. Patients were identified through computer-generated daily microbiology reports. The patients who had blood culture reports of VRE on weekends or holidays were followed from the nearest workday. VRE bacteraemia was defined as the growth of VRE in one or more blood culture from a patient with fever (body temperature ≥38°C). If the patient had multiple episodes of VRE bacteraemia during the study period, only the first episode was included. Patients who had VRE bacteraemia and were prescribed parenteral daptomycin or linezolid were included. The decision about which drug to use and the dose for each patient was made by the primary care physician. There were no local guidelines for using a higher dose of daptomycin for the treatment of more severe infection. If a patient initially received daptomycin but this was later changed to linezolid, that patient was placed into the daptomycin group, and vice versa. Patients who were younger than 18 years of age, who were not admitted to hospital, who received <6 mg/kg of daptomycin or who received daptomycin and linezolid in combination were excluded.

Microbiologic studies and antimicrobial susceptibility testing

Blood cultures were processed by the clinical microbiology laboratory. VRE was identified using the VITEK-2 identification system (bioMérieux, Marcy l'Etoile, France). Vancomycin resistance was defined as an enterococcus isolate with a minimum inhibitory concentration (MIC) of vancomycin of ≥32 mg/L. The blood isolates were preserved for subsequent microbiologic characterization. The MICs of linezolid and daptomycin against enterococci were determined using the broth microdilution method and interpreted according to the Clinical and Laboratory Standards Institute [20].

Clinical data collection and definitions

We prospectively followed the patients daily by reviewing the electronic medical records and recorded the patients' demographic data, underlying diseases and sites of infection. The sites of primary infection were identified according to the definitions of the US Centers for Disease Control and Prevention [21]. If no infectious focus of bacteraemia could be identified, the bacteraemia was classified as primary bacteraemia. The Charlson comorbidity index was used to adjust for underlying conditions [22]. Bacteraemia severity was assessed using the Pitt bacteraemia score at the onset of bacteraemia [23].

Bacteraemia onset was defined as the day when the VRE-positive sample for blood culture was drawn. The daptomycin dose was calculated according to the subject's actual body weight. Use of immunosuppressive agents was defined as the receipt of antineoplastic drugs, cyclophosphamide or other immunosuppressive agents within 6 weeks, or as receipt of prednisolone at a dosage of ≥20 mg daily for ≥2 weeks or 30 mg daily for ≥1 week before onset of bacteraemia. Thrombocytopaenia was defined as a platelet count <80 000/μL. We recommended that the creatine phosphokinase (CPK) level be measured at least once a week during daptomycin treatment [24] and if symptomatic in either group of patients. Elevated CPK was defined as CPK higher than the upper limit of normal. High elevation of CPK was defined as CPK more than tenfold the upper limit of normal. Creatinine clearance was estimated using Cockcroft-Gault equation [25,26]. Augmented renal clearance (ARC) was defined as creatinine clearance ≥130 (mL/min/1.73 m^2) [26]. The primary outcome was all-cause in-hospital 14-day mortality after the onset of VRE bacteraemia. Secondary outcomes included infection-related mortality, adverse events such as thrombocytopaenia and elevated CPK. Infection-related mortality was defined as death within 14 days after onset of VRE bacteraemia without another explanation and without resolution of infection symptoms or signs, or persistent VRE bacteraemia before death.

Statistical analysis

The mean and SD were calculated for continuous variables and percentages for categorical variables. Student's *t* test and Fisher's exact test were used to compare continuous and categorical variables, respectively, between two groups. Multivariate logistic regression was used for outcome analysis. Variables with p ≤0.2 in the univariate regression were included in the multivariate analysis. Multivariable models were developed by backward stepwise minimizing Akaike's information criterion (AIC) [27]. After stepwise AIC selection, only variables with p ≤0.05 were considered significant and were retained in the final multivariate prediction model. The dose–response relationship between the daptomycin dose and mortality was estimated using the generalized additive model (GAM) [28]. Propensity score–matched analyses were performed as sensitivity analysis [29]. Stata 14 (StataCorp, College Station, TX, USA) was used. Two-sided p values of ≤0.05 were considered significant.

Results

Two hundred twelve patients were enrolled in 2010–2015 (Fig. 1). All patients had vancomycin-resistant *Enterococcus faecium* infection, and three had vancomycin-resistant *Enterococcus faecalis* coinfection. The mean (SD) age of the study cohort was 65.1 (17.1) years, and Pitt bacteraemia score was 3.7 (2.8) points. One hundred twenty-three patients (58%) were men, and 89 (42.0%) used an immunosuppressive agent (Table 1). Linezolid and daptomycin MICs were available in 177 VRE isolates. No linezolid resistance was found in VRE isolated from patients receiving linezolid treatment, but two VRE isolates from patients receiving daptomycin showed daptomycin resistance.

Five of the 141 daptomycin-treated patients had changed to linezolid treatment because of a lack of improvement (five patients had microbiology-documented failure and persistent VRE bacteraemia under daptomycin treatment). Seven of the 71 linezolid-treated patients had changed to daptomycin treatment (four due to thrombocytopaenia, one due to suspicious linezolid-related

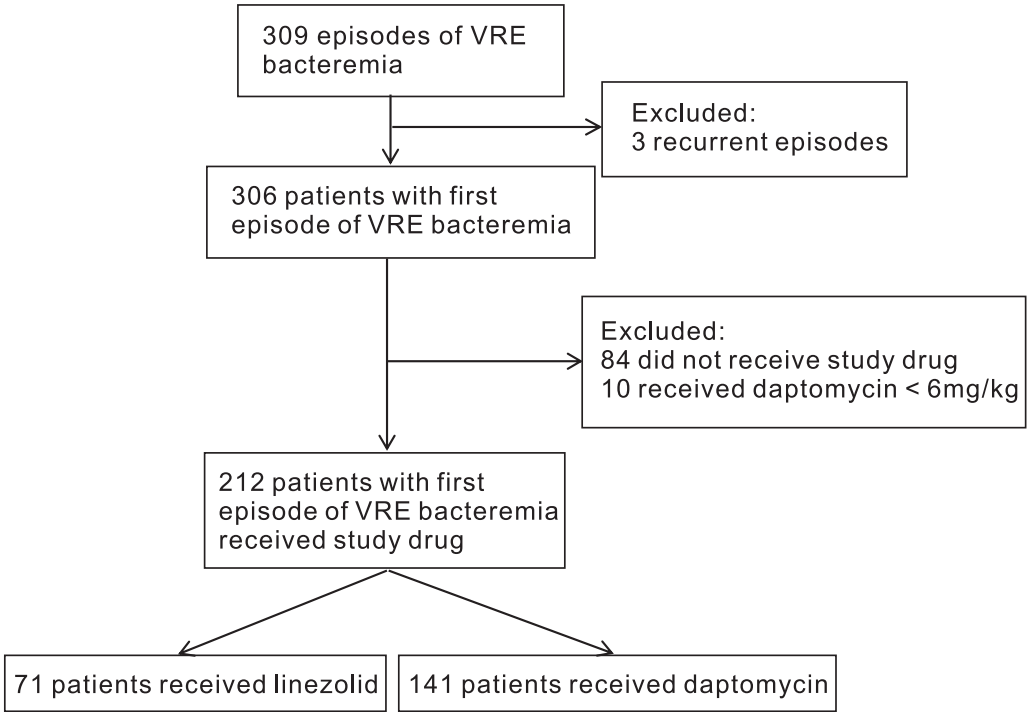

Fig. 1. Flow diagram illustrating selection of study patients.

abnormal liver function and two due to clinical suspected poor response).

The patients' baseline characteristics differed between the daptomycin and linezolid groups (Table 1). Although the Pitt bacteraemia score, the Charlson score and the time to effective antimicrobial therapy did not differ between the daptomycin and linezolid groups, the daptomycin group had a higher all-cause 14-day mortality (36.9% vs. 21.1%; p 0.03) and infection-related mortality (38.3% vs. 21.1%; p 0.01). The daptomycin group also had a trend towards higher all-cause 28-day mortality and all-cause in-hospital mortality (p 0.15 and p 0.18, respectively). There was no significant elevation of CPK or thrombocytopaenia differences between the daptomycin and linezolid groups (p 0.78 and p 0.30, respectively) (Table 1). One patient in the linezolid group had elevated CPK after antimicrobial therapy was changed to daptomycin. Only one patient, who was in the lower-dose daptomycin group, had high CPK elevation.

Mortality analysis

In the univariate analysis, significant variables associated with all-cause 14-day mortality were daptomycin use, bacteraemia severity (indicated by the Pitt bacteraemia score and thrombocytopaenia), catheter-related infection and steroid use. After considering the above covariates as well as those variables in the univariate analysis with p <0.2 in the multivariate stepwise logistic regression analysis, linezolid use predicted lower all-cause 14-day mortality compared to daptomycin (adjusted odds ratio (aOR), 0.45; 95% confidence interval (CI), 0.21–0.96; p 0.04) (Table 2). Linezolid use also predicted lower infection-related mortality compared to daptomycin (aOR, 0.46; 95% CI, 0.22–0.96; p 0.04).

Association between daptomycin dose and mortality

Among daptomycin-treated patients, higher-dose daptomycin (per 1 mg/kg) was significantly associated with lower all-cause 14-day mortality (odds ratio, 0.76; 95% CI, 0.59–0.98; p 0.03). The GAM was used to determine the dose–response relationship between the daptomycin dose and mortality; it showed lower mortality in patients who received higher-dose daptomycin (Supplementary Fig. 1). Using the GAM results, a daptomycin dose of ≥9 mg/kg was selected as the cutoff between the lower and higher doses (Supplementary Fig. 1).

There was no significant difference of the patients' baseline characteristics and disease severity between the lower-dose and higher-dose daptomycin-treated patients, except that the lower-dose group weighed more (59.6 kg vs. 52.3 kg; p <0.001) (Supplementary Table 1). Fifteen (21.3%) linezolid-treated patients died, eight (23.5%) of 34 higher-dose daptomycin-treated patients died and 44 (41.1%) of 107 lower-dose daptomycin-treated patients had 14-day mortality (p 0.01). In the univariate analysis, compared to daptomycin dose 6 to 9 mg/kg, both daptomycin dose ≥9 mg/kg (odds ratio, 0.44; 95% CI, 0.18–1.06; p 0.07) and linezolid (odds ratio, 0.38; 95% CI, 0.19–0.76; p 0.006) were associated with lower all-cause 14-day mortality. In the multivariate logistic regression analysis, linezolid use (aOR, 0.36; 95% CI, 0.17–0.79; p 0.01) and higher-dose daptomycin (aOR, 0.26; 95% CI, 0.09–0.74; p 0.01) predicted lower 14-day mortality compared to lower-dose daptomycin. Compared to higher-dose daptomycin, linezolid conferred no survival benefit (aOR, 1.40; 95% CI, 0.45–4.37; p 0.57).

Sensitivity analysis

Multivariate logistic regression was used to identify independent variables associated with the choice of linezolid rather than daptomycin for subsequent propensity score matching analysis. Factors associated with linezolid use were underlying cerebral vascular disease (aOR, 2.28; p 0.05), heavier body weight (aOR, 1.04; p 0.007) and no leukopenia (aOR, 5.4; p 0.001). Using propensity score matching, we matched 66 pairs of patients provided linezolid or daptomycin to treat VRE bacteraemia. After matching, the potential prognostic factors and severity of illness did not differ

Table 1
Demographics and clinical characteristics of patients with vancomycin-resistant enterococcal bacteraemia

Characteristic[a]	Daptomycin ($n = 141$)	Linezolid ($n = 71$)	p
Demographics			
Age, y	64.4 (17.9)	66.6 (15.5)	0.40
Male	78 (55.3)	45 (63.4)	0.30
Body weight, kg	57.9 (11.2)	61.6 (14.0)	0.04
Days of prior hospitalization	33.1 (32.2)	32.0 (35.2)	0.82
Underlying condition			
Charlson score	2.9 (2.5)	4.0 (2.5)	0.77
Congestive heart failure	8 (5.7)	9 (12.7)	0.10
Cerebrovascular disease	16 (11.3)	15 (21.1)	0.07
Autoimmune disease	4 (2.8)	1 (1.4)	0.67
Liver cirrhosis	25 (17.7)	19 (26.8)	0.15
Diabetes mellitus	43 (30.5)	26 (36.6)	0.44
Chronic kidney disease	43 (30/5)	25 (35.2)	0.53
Malignancy	77 (54.6)	26 (36.6)	0.01
Use of immunosuppressive agents	66 (46.8)	23 (32.4)	0.06
Steroid	22 (15.6)	10 (14.1)	0.84
Chemotherapy	51 (36.2)	14 (19.7)	0.02
Infection focus			
Primary bacteraemia	95 (67.4)	38 (53.5)	0.05
Catheter-related infection	12 (8.5)	9 (12.7)	0.34
Urinary tract infection	21 (14.9)	12 (16.9)	0.69
Intra-abdominal infection	11 (7.8)	7 (9.9)	0.61
Surgical site infection	5 (3.6)	5 (7.0)	0.31
Clinical characteristic			
White blood cell count ($\times 10^3/\mu L$)	11.5 (13.2)	13.3 (8.7)	0.30
Leukopenia (<4000/μL)	40 (28.4)	5 (7.0)	<0.001
Platelet count ($\times 10^3/\mu L$)	120.1 (109.0)	163.9 (128.1)	0.01
Thrombocytopaenia (<80 000/μL)	72 (51.1)	20 (28.2)	0.002
Creatinine clearance (mL/min/1.73 m^2)	34.9 (26.9)	31.5 (24.5)	0.37
Ventilator use	60 (42.6)	34 (47.9)	0.47
Pitt bacteraemia score	3.6 (3.0)	3.8 (2.5)	0.65
Pitt bacteraemia score ≥3	76 (55.1)	47 (66.2)	0.14
Days to effective antimicrobial therapy	3.2 (1.9)	3.1 (2.5)	0.56
Antibiotics dose (mg/kg or mg every 12 hours)	7.9 (1.4)	600	
Outcome			
All-cause in-hospital mortality	90 (63.8)	38 (53.5)	0.18
All-cause 28 d mortality	69 (48.9)	27 (38.0)	0.15
All-cause 14 d mortality	52 (36.9)	15 (21.1)	0.03
Infection-related mortality	54 (38.3)	15 (21.1)	0.01
Switch to other group	5 (3.6)	7 (9.9)	0.11
Lack of improvement	5 (3.6)	2 (2.8)	0.99
Adverse event	0 (0)	5 (7.0)	0.004
Elevated creatinine kinase	10 (7.1)	4 (5.6)	0.78
Thrombocytopaenia[b]	16 (23.2)	17 (33.3)	0.30

[a] Data are mean (SD) for continuous variables and *n* (%) for categorical variables, with two-tailed Student's *t* test used for the former and Fisher's exact test for the latter.
[b] Among patients who were nonthrombocytopenic before treatment.

significantly between the two groups. The propensity scores were 0.381 for daptomycin and 0.385 for linezolid (p 0.58).

Of the 66 pairs of patients included in the propensity score matching analysis, 13 (19.7%) linezolid-treated patients died, 3 (25%) of 12 higher-dose daptomycin-treated patients died, and 24 (44.4%) of 54 lower-dose daptomycin-treated patients died. Linezolid treatment independently predicted lower mortality compared to daptomycin in the matched cohort (aOR, 0.39; 95% CI, 0.18–0.85; p 0.02). Linezolid use independently predicted lower mortality compared to lower-dose daptomycin in the matched patients (aOR, 0.34; 95% CI, 0.14–0.79; p 0.01). Linezolid treatment was not significantly superior to higher-dose daptomycin in terms of mortality (aOR, 0.98; 95% CI, 0.14–7.03; p 0.99) in the matched cohort.

Discussion

We found a dose-dependent clinical response of daptomycin. Mortality was lower in patients treated with the higher dose compared to the lower dose of daptomycin. Although all daptomycin-treated patients received ≥6 mg/kg daptomycin, this group experienced worse clinical outcomes than the linezolid group. Mortality was higher in the group treated with lower-dose daptomycin (6–9 mg/kg) than in the linezolid-treated group. However, there was no difference in survival between the higher-dose daptomycin-treated group (≥9 mg/kg) and the linezolid-treated group. These findings suggest that the currently recommended daptomycin dose might be suboptimal for the treatment of VRE bacteraemia.

Since 2009, several studies have discussed the effectiveness of daptomycin in treating VRE bacteraemia [8,11–16], although the results are conflicting [8–10,19]. One possible explanation for the conflicting results relates to the daptomycin and linezolid doses. Daptomycin exhibits rapid concentration-dependent bactericidal activity *in vitro* against Gram-positive organisms, including enterococci [30]. A daptomycin dose of ≤8 mg/kg might not induce sustained bactericidal activity, whereas ≥10 mg/kg does [31]. A previous case series noted better outcomes for patients provided daptomycin at a dose of >6 mg/kg [18]. The daptomycin dose has varied widely in previous studies (3.4–10.4 mg/kg) [13,16,32,33]. Some patients may have been underdosed. By contrast, the median daptomycin dose used in the study by Britt *et al.* [8] was 5.93 mg/kg (interquartile range, 5.33–6.10 mg/kg) which is more consisted to the recommended dose of 6 mg/kg. We used a minimum

Table 2
Logistic regression analysis of the associated with 14-day mortality

Characteristic	Univariate		Multivariate[a]	
	Crude odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)	p
Demographics				
Age	1.01 (0.99–1.03)	0.29		
Male	1.01 (0.56–1.82)	0.97		
Body weight	1.01 (0.99–1.04)	0.21		
Days of prior hospitalization	1.00 (0.99–1.01)	0.97		
Underlying condition				
Charlson score	1.04 (0.93–1.16)	0.53		
Congestive heart failure	0.64 (0.20–2.06)	0.46		
Cerebrovascular disease	1.04 (0.46–2.34)	0.93		
Autoimmune disease	1.46 (0.24–8.93)	0.68		
Liver cirrhosis	1.01 (0.50–2.07)	0.97		
Diabetes mellitus	1.02 (0.55–1.89)	0.95		
Chronic kidney disease	1.16 (0.63–2.15)	0.63		
Malignancy	1.04 (0.58–1.86)	0.90		
Use of immunosuppressive agents	1.69 (0.94–3.03)	0.08		
Steroid	4.02 (1.84–8.76)	<0.001	3.43 (1.42–8.31)	0.006
Chemotherapy	1.16 (0.62–2.16)	0.64		
Infection source				
Primary bacteraemia	0.83 (0.46–1.50)	0.54		
Catheter-related infection	2.65 (1.07–6.60)	0.04		
Urinary tract infection	1.50 (0.70–3.24)	0.30		
Intra-abdominal infection	0.59 (0.19–1.88)	0.38		
Surgical site infection	0.53 (0.11–2.55)	0.43		
Clinical characteristic				
White blood cell count ($\times 10^3/\mu L$)	1.02 (0.99–1.04)	0.15		
Leukopenia (<4000/μL)	0.97 (0.48–1.98)	0.94		
Platelet count ($\times 10^4/\mu L$)	0.93 (0.90–0.97)	<0.001	0.94 (0.91–0.98)	0.002
Thrombocytopaenia (<80 000/μL)	2.65 (1.46–4.80)	0.001		
Ventilator use	1.22 (0.68–2.19)	0.50		
Pitt bacteraemia score	1.26 (1.13–1.41)	<0.001	1.27 (1.13–1.43)	<0.001
Pitt bacteraemia score ≥3	3.24 (1.67–6.29)	0.001		
Days to initiate effective antimicrobial therapy	0.89 (0.77–1.03)	0.11		
Linezolid vs. daptomycin	0.46 (0.24–0.89)	0.02	0.45 (0.21–0.96) [b]	0.04
Reference: daptomycin use, dose 6–9 mg/kg[a]				
Daptomycin use, dose ≥9 mg/kg	0.44 (0.18–1.06)	0.07	0.26 (0.09–0.74)	0.01
Linezolid use	0.38 (0.19–0.76)	0.006	0.36 (0.17–0.79)	0.01

[a] Multivariate logistic regression model, with daptomycin dose considered in the model: $n = 212$, Nagelkerke/Cragg and Uhler's $R^2 = 0.318$, deviance goodness-of-fit (GOF) test, p 0.33 > 0.05; Hosmer and Lemeshow GOF test, p 0.12 > 0.05; estimated area under the ROC curve = 0.79.
[b] If daptomycin dose was not considered in the model.

daptomycin dose of 6 mg/kg, and the linezolid group had better clinical outcomes on average. The higher-dose daptomycin group (≥9 mg/kg) had a similar outcome or trend towards a better outcome compared to linezolid treatment.

In addition, although linezolid 600 mg every 12 hours was used in our study and the study by Britt *et al.* [8], Cai *et al.* [34] showed that the inhibitory activity was lower in heavier patients (>80 kg) and recommended adjusting the dose by body weight to 10 mg/kg. In the linezolid-treated group in our study, only five patients weighed >80 kg. Body weight seemed to be higher in the study by Britt *et al.* compared to our linezolid-treated group (mean body mass index, 25.5 and 23.3 kg/m^2, respectively). Therefore, the clinical effectiveness of linezolid might have been lower in heavier patients in the study by Britt *et al.*

All of the VRE bacteraemia treatment studies were retrospective cohort studies. The study by Britt *et al.* [8] is important because it included the largest sample size and had a relatively good design. However, the study by Britt *et al.* differed from the other studies. For example, the reported Charlson score was 9 in the study by Britt *et al.*, which was higher than the scores of 4 to 5 in other studies [15,32,35,36]. The length of hospital stay before bacteraemia was only 5 days in the study by Britt *et al.*, which was shorter than the 18 to 30 days in other studies [13,32,36]. The large differences in patient characteristics between the study by Britt *et al.* and other studies might reflect heterogeneity between studies, which makes it difficult to make direct comparisons. In addition, the study by Britt *et al.* is limited by the patients enrolled being nearly all male, as the study was based in American Veterans Association medical centres and contained relatively few transplant recipients; therefore, the result is not likely to be generalized to all medical centres [37].

Higher-dose daptomycin is used to treat Gram-positive and enterococcal infections, and it is generally safe [38–40]. In our study, two (5.9%) of the higher-dose daptomycin-treated and eight (7.4%) of the lower-dose-treated patients exhibited an elevated CPK level (p 0.99). Although an elevated CPK level might relate more to the dosing interval rather than the peak daptomycin concentration [41], and although a prior study also demonstrated that a higher daptomycin dose (>8 mg/kg) did not correlate with the highest observed CPK level [40], a report has demonstrated that higher-dose daptomycin might cause a higher percentage of patients to exhibit elevated CPK level [24]. Therefore, we suggest that higher-dose daptomycin be used in the treatment of VRE bacteraemia, but the CPK level should be monitored closely until sufficient experience proves that higher-dose daptomycin is as safe as the lower dose.

Daptomycin is cleared by the kidneys, and patients with ARC might eliminate certain antibiotics more quickly. However, because therapeutic drug monitoring was not performed, we do not know whether ARC affected the initial C_{max} of daptomycin and affected mortality. We analysed the creatinine clearance (mL/min/1.73 m^2) and the association of all-cause 14-day mortality. The mean (SD)

creatinine clearance of the survival group was 36.2 (28.0) and of the mortality group was 28.7 (20.8) (p 0.05). Only one patient with ARC, who was in the lower-dose daptomycin group, did not have 14-day mortality. We therefore cannot demonstrate that ARC was associated with higher 14-day mortality. Renal clearance was more likely to be an indicator of underlying morbidity; better renal clearance is associated with good clinical outcome, though this variable was not significant in our multivariate analysis.

This study has several limitations. Firstly, because there was no therapeutic drug monitoring of daptomycin, we were unable to show that a better pharmacodynamic parameter (peak/MIC or 24-hour area under the curve/MIC) is associated with better outcome. Secondly, although the multivariate regression approach and propensity score matching showed consistent results, there may have been unmeasured confounders not examined in our study. Thirdly, this was an observational study, and the follow-up bacterial culture was dependent on the primary care physician; therefore, we could not evaluate differences in the microbiologic responses between daptomycin and linezolid treatment of VRE bacteraemia. Finally, the higher-dose cutoff was chosen using the statistical approach and should be validated in further clinical studies.

In conclusion, daptomycin displays a dose-dependent clinical response. Higher-dose daptomycin was associated with better survival than lower-dose daptomycin. Although the lower-dose daptomycin group (6–9 mg/kg) had worse clinical outcome than the linezolid group, the linezolid group had no survival benefit compared to the higher-dose daptomycin group (≥9 mg/kg). Further studies are needed to determine the adequate daptomycin dose for treating VRE bacteraemia. Larger randomized control trials with higher-dose daptomycin are needed to compare the efficacy of daptomycin and linezolid in treating VRE bacteraemia.

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Transparency Declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2016.07.018.

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