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Association between daptomycin dosing and in-hospital mortality in patients with vancomycin-resistant *Enterococcus faecium* bloodstream infection

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Background: Vancomycin-resistant *Enterococcus faecium* (VRE*fm*) bloodstream infections (BSIs) pose significant management challenges with uncertainties relating to the optimal daptomycin dose for treatment.

Methods: A retrospective cohort study of adult patients receiving ≥3 days of definitive treatment for a first episode VRE*fm* BSI between 2015 and 2022 was undertaken. Daptomycin doses were classified as low (≤7.9 mg/kg), medium (8.0 to 9.9 mg/kg) or high (≥10 mg/kg). We aimed to assess the association between daptomycin dose and in-hospital 30-day all-cause mortality in addition to other clinical outcomes (hospital length of stay, transfer to the ICU within 48 hours and microbiological failure). In addition, we undertook a comparative analysis of mortality and other outcomes in *vanB* VRE*fm* BSIs receiving definitive daptomycin and teicoplanin treatment.

Results: A total of 191 patients received definitive daptomycin ($n=111$) or teicoplanin ($n=80$) therapy and were included in two separate analyses. Of the 111 daptomycin patients, most received high-dose daptomycin (59.5%), with 29.7% and 10.8% receiving medium and low doses, respectively. All-cause 30-day in-hospital mortality was 17.1% and there was no association between daptomycin dose groups and in-hospital 30-day mortality (log rank $P=0.369$). Microbiological failure was associated with dose ($P=0.036$): 33.3% in the low dose group, 12.1% for medium and 19.7% for high. No mortality difference was observed between *vanB* VRE*fm* BSIs treated with daptomycin or teicoplanin [adjusted cause-specific hazard ratio 0.67 (95% CI: 0.28–1.59)].

Conclusions: In this contemporary study of predominantly high daptomycin doses, there was no association between daptomycin dose and 30-day in-hospital mortality but we did observe an association with microbiological failure.

Introduction

Vancomycin-resistant *Enterococcus faecium* (VRE*fm*) bloodstream infections (BSIs) pose a significant challenge for management within the healthcare environment. They disproportionately affect sicker patients, have a high mortality (up to 45%) and have only a limited number of effective treatment options available.[1]

Daptomycin is considered one of the key antibiotic agents for the management of VRE*fm* BSIs, despite not being approved for this indication. Daptomycin is a cyclic lipopeptide antibiotic agent with a bactericidal, dose-dependent effect on VRE BSIs.[2]

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Standard dosing of daptomycin (4 to 6 mg/kg) is approved for the treatment of *Staphylococcus aureus* infections, however, studies demonstrate that higher daptomycin doses are associated with improved survival for VRE BSIs when compared with lower doses.[3–6]

Australia has seen a significant increase in vancomycin resistance in *E. faecium* (VRE*fm*) BSIs since it was first identified in 1994, and now has one of the highest rates globally. In 2023, 50.8% of *E. faecium* isolates in blood were phenotypically resistant to vancomycin, with *vanB* being the predominant genotype.[7] Daptomycin is routinely used as one of the first-line agents for the treatment of VRE*fm* infections worldwide. EUCAST, however, does not provide breakpoints for enterococci due to the uncertainty about achieving adequate daptomycin exposure with high daptomycin doses.[8] By contrast, CLSI provides two sets of breakpoints: one for *Enterococcus* spp. other than *E. faecium* [Susceptible (S) ≤2, Intermediate (I) = 4, Resistant (R) ≥8 μg/mL] and the other for serious infections due to *E. faecium* [Susceptible dose dependent (SDD) ≤4, R ≥ 8 μg/mL].[9] For *vanB* VRE BSIs, teicoplanin is an alternate treatment option in Australia. EUCAST provide clinical breakpoints for teicoplanin (S ≤ 2 mg/L, R > 2 mg/L), although warn that enterococci harbouring *vanB* may appear susceptible, but resistance may develop during therapy.[10,11] Teicoplanin is considered an investigational agent by CLSI with different clinical breakpoints (S ≤ 8 μg/L, I = 16, R ≥ 32 μg/mL). Thus far, there has not been a comparison of patient outcomes between teicoplanin and daptomycin for *vanB* VRE BSIs.

There is a lack of published studies evaluating the dose/outcome relationship of daptomycin treatment of VRE*fm* infections in patient populations predominated by *vanB* resistance determinants. Given this lack of evidence and the uncertainties relating to the optimal daptomycin dose for VRE*fm* BSIs (irrespective of genotype), we (i) assessed the association between daptomycin dose and 30-day all-cause mortality (primary outcome) in addition to other clinical outcomes, including hospital length of stay, requirement for transfer to ICU within 48 hours and microbiological failure for patients with VRE*fm* BSIs (irrespective of genotype), and (ii) determined whether there is a difference in 30-day all-cause mortality and other clinical outcomes in patients with *vanB* VRE*fm* BSIs receiving definitive teicoplanin or daptomycin therapy.

Patients and methods

Setting

Our centre is a quaternary referral hospital in metropolitan Melbourne with ~600 acute inpatient and 62 ICU beds. The hospital provides a number of state-wide services including lung, heart, kidney and bone marrow transplant, trauma and burns management. The onsite clinical microbiology diagnostic laboratory uses the BD BACTEC™ (Ontario, Canada) automated blood culture incubation system and performs *vanA/B* PCR (Cepheid Xpert®, USA) on all enterococci isolated from blood. Chromogenic media (e.g. Brilliance™ VRE, Thermo Fisher Scientific, USA) was used to confirm vancomycin resistance on duplicate isolates from repeat cultures. Antimicrobial susceptibility testing was performed by VITEK®2 AST-P643 (bioMerieux, France). Interpretation of results apply EUCAST breakpoints. When performed, MIC was determined by gradient strip (ETEST®, bioMérieux, France) following the manufacturer's guidelines. CLSI interpretations were used for reporting daptomycin susceptibility until June 2020, at which time reporting was changed to report the MIC value without a susceptibility categorization reported to reflect the EUCAST guidance.[8] Daptomycin wild-type isolates were defined using the EUCAST epidemiological cut-off value (ECOFF) MIC ≤8 mg/L. Routine VRE screening is not undertaken at our institution. This study was reviewed and approved by the Human Research and Ethics Committee at Alfred Health (reference number 169/23) and Monash University.

Study population and design

A retrospective cohort study was undertaken in adult patients receiving ≥3 days of treatment for an index VRE*fm* BSI between 2015 and 2022. Patients were included if their first positive blood culture was collected while being cared for at The Alfred hospital and follow-up continued until they were discharged from hospital. Patients were excluded if they had a first positive blood culture at another hospital or were transitioned to end-of-life care within the first 3 days of BSI treatment.

Study outcomes and definitions

The primary study outcome was to assess the association between daptomycin dose groups and in-hospital 30-day all-cause mortality, measured from the day of the first positive blood culture for VRE*fm*. Secondary outcome measures included time to administration of active antibiotic therapy, hospital length of stay post positive index blood culture, requirement for transfer to the ICU within 48 hours following the index blood culture being drawn, the proportion of patients experiencing microbiological failure (defined as persistent VRE*fm* BSI, relapse VRE*fm* BSI or persistent plus relapse VRE*fm* BSI recurrence), and the incidence of daptomycin related adverse effects.

Active antibiotic therapy was defined as receipt of an antibiotic agent with phenotypic susceptibility to the VRE*fm* isolate. Definitive antibiotic treatment was defined as the first active antibiotic agent that was administered ≤96 hours from the index blood culture being drawn, and was continued for ≥3 consecutive days. Daptomycin doses were calculated by averaging the milligram per kilogram per day dose received for the first 3 days that met criteria for definitive therapy and were classified as low (≤7.9 mg/kg), medium (8.0–9.9 mg/kg) or high (≥10 mg/kg). Doses were calculated using actual body weight. The Pitt Bacteraemia Score was used as an indicator of illness severity.[12] Table S1 (available as Supplementary data at *JAC-AMR* Online) provides definitions for blood culture clearance, persistent BSI, relapse BSI, daptomycin 'dosing weight', concurrent beta-lactam therapy, time to active antibiotic therapy, source of the VRE*fm* BSI, acute kidney injury, creatinine phosphokinase (CPK) elevation and eosinophilic pneumonia.

Statistical analysis

Categorial data are presented as frequency with percentage and continuous data as means with standard deviation or median with IQR, depending on distribution. Comparisons between groups were made using a Fisher's exact test, Mann–Whitney *U*-test or Kruskal–Wallis test, as appropriate. Cause-specific Cox proportional-hazards regression models were used to quantify the impact of dose groups on the competing events of 30-day in-hospital mortality and discharge from hospital alive. Patients who were discharged before 30 days were censored as a competing event in the mortality model. Discharge after 30 days was censored at 30 days. Mortality was censored similarly for the discharge alive model. Time was measured in days from blood culture collection. Multivariable mortality models included Pitt Bacteraemia Score (continuous) as an indicator of severity and also explored other potential risk factors by assessing variables that were associated with the outcome at $P < 0.05$ in the univariate analysis. Due to small numbers and to avoid overfitting, a stepwise approach was used so that only variables significant at $P < 0.05$ were

retained in the final adjusted model. The same approach was used to assess association between all-cause 30 day in-hospital mortality and treatment groups for *vanB* VRE*fm* BSIs. The proportional-hazards assumption was assessed using Schoenfeld residuals. Interaction between dose groups and severity of illness was explored and included if the terms provided a better model fit according to a lower Akaike's information criterion. Data analysis was performed using Stata v.17.0 (College Station, TX, USA).

Results

Between 2015 and 2022 there were 824 enterococcal BSIs on which antibiotic susceptibility was performed (Figure 1), including 377 vancomycin susceptible isolates. After removing exclusions, including non-*E. faecium* isolates, duplicate cultures and those that did not meet the definition of definitive therapy, 256 eligible patients with a first episode VRE*fm* isolate were eligible for inclusion. Of these, 191 patients received definitive daptomycin ($n=111$) or teicoplanin ($n=80$) therapy and were included in two separate analyses (Figure 1).

Study population and demographics (daptomycin cohort, n = 111 patients)

The baseline demographics for patients according to daptomycin dose group is shown in Table 1. Patients were predominantly male (67.6%) with a median age of 63 years (IQR: 47 to 70 years). The median total body weight was 74.0 kg (IQR: 64.3 to 88.0 kg), with 25.2% of patients classified as obese (BMI ≥30 kg/m2) on the day of index blood culture collection. The most common source of VRE*fm* BSI was primary BSI (42.3%), followed by line associated (28.8%) and intra-abdominal (20.7%). BSIs occurred at

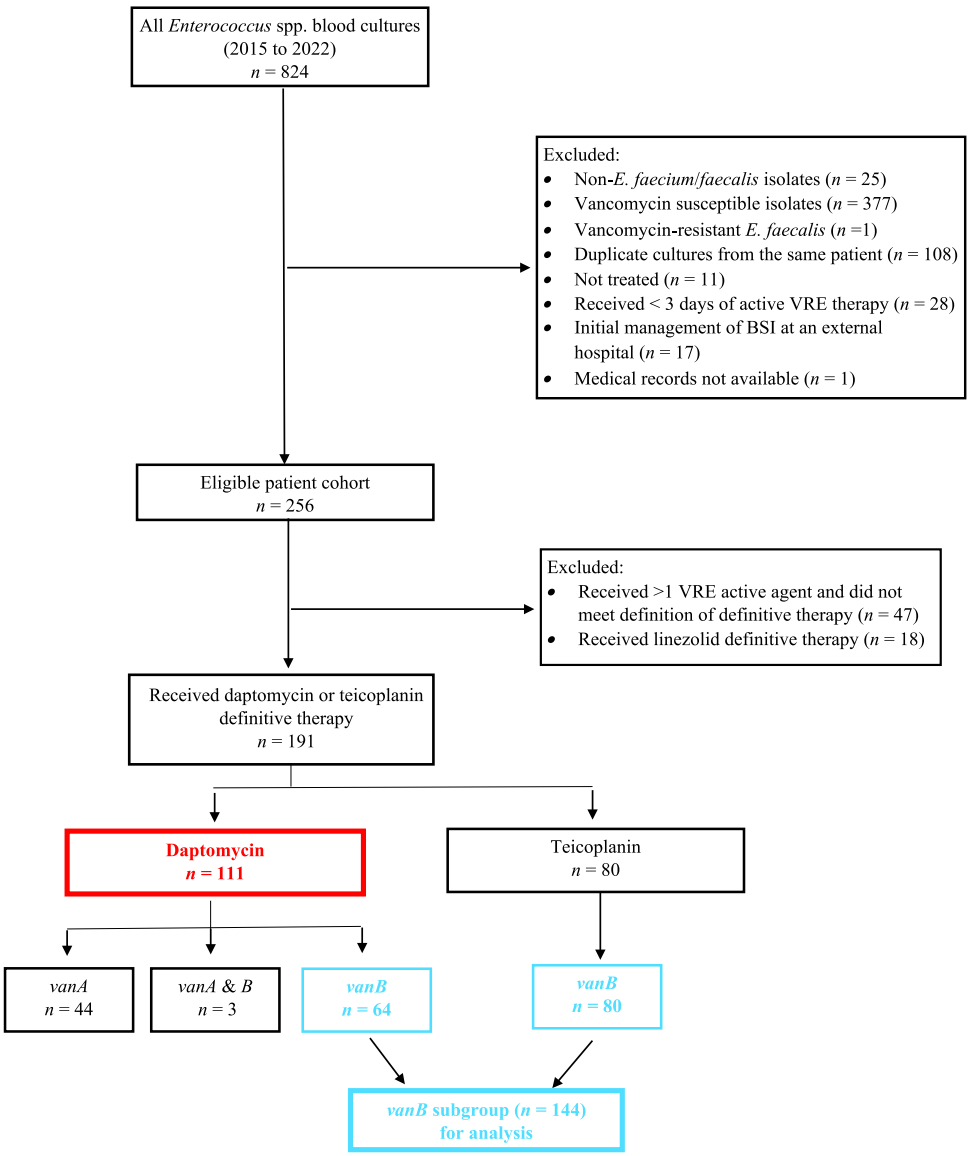

Figure 1. Flow diagram illustrating selection of patients for inclusion.

a median of 17.0 days following hospital admission (IQR: 13.0 to 24.0 days), with 93.7% ($n=104$) considered hospital acquired (onset ≥48 hours after admission). Almost all patients (99.1%) received input from the Infectious Diseases (ID) Unit during their infection.

Comorbidity and illness severity (daptomycin cohort, n = 111 patients)

Neutropenia (neutrophils $<0.5\times10^9$/L) on the day of blood culture draw was present in 61.3% of patients, while 18.0% of patients were in the ICU (Table 1). Fourteen patients (12.6%) were on renal replacement therapy on the day of index positive blood culture, with most (78.6%) being on continuous renal replacement therapy (CRRT). The median Pitt Bacteraemia Score was 1.0 (IQR: 0 to 2.0).

Microbiology (daptomycin cohort, n = 111 patients)

Most blood cultures were monomicrobial (91%). Only 11.7% of patients ($n=13$) were known to be colonized with VRE before the index BSI. BSIs were predominantly caused by the *vanB* genotype ($n=64$, 57.7%), while 39.6% were *vanA*, and 2.7% harboured both *vanA* and *vanB* genes. Daptomycin MIC was available in 109 isolates, with all isolates being wild-type.

Daptomycin treatment

The median dose of daptomycin definitive therapy was 10.2 mg/kg (IQR: 9.6 to 11.0 mg/kg, Table 1). Most patients received high-dose daptomycin (≥10 mg/kg; 59.5%), whereas 29.7% and 10.8% were classified as receiving medium (8–9.9 mg/kg) and low (≤7.9 mg/kg) dosing, respectively (Table 1). The median time to administration of daptomycin was 35.9 hours (IQR: 23.6 to 46.1 hours) from index positive blood culture draw. Total BSI treatment duration was for a median duration of 12.9 days (IQR: 10.4 to 16.4 days).

Clinical outcomes (daptomycin cohort, n = 111 patients)

Daptomycin dose and 30-day in-hospital mortality

Unadjusted all-cause 30-day in-hospital mortality was 17.1% ($n=19$). The Kaplan–Meier estimator for overall survival by 30-days was 73.8% (95% CI: 60.9 to 82.9%); 65.6% (95% CI: 15.7 to 90.9%) for the low dose group, 86.9% (95% CI: 64.3 to 95.6%) for the medium dose group and 69.0% (95% CI: 52.0 to 81.1%) for the high-dose group (Figure 2). There were 60 patients who were discharged alive before 30 days who were censored as a competing event. There was no association between low, medium or high daptomycin dose groups and 30-day in-hospital mortality (Figure 2, log rank $P=0.369$ and Table 2). Results were similar when daptomycin doses were calculated according to dosing weight ($P=0.54$), as a continuous variable ($P=0.51$) or as a dichotomous variable (doses ≥10 versus <10 mg/kg; $P=0.205$; Table S2). The competing event of discharge alive was also not associated with dose groups (Table S3).

Factors associated with 30-day in-hospital mortality

On univariate analysis, 30-day in-hospital mortality was significantly associated with presence of renal replacement therapy, higher neutrophil count, more timely administration of daptomycin therapy, elevation in CPK and development of acute kidney injury (from any cause) (Table 2). All-cause in-hospital mortality by 30-days was also associated with several illness severity proxies, including location in ICU at the time of index positive blood culture, transfer to ICU within 48 hours of the index blood culture being drawn and Pitt Bacteraemia Score. However, only Pitt Bacteraemia Score was included as this was specified *a priori* and all the severity indicators were significantly correlated with each other. Higher neutrophil count [adjusted cause-specific hazard ratio (AcsHR): 1.11, 95% CI, 1.03 to 1.19], more timely administration of daptomycin (AcsHR: 0.96, 95% CI, 0.93 to 0.99) and development of an acute kidney injury (aHR: 7.33, 95% CI, 2.03–26.5) were significantly associated with mortality in the multivariable model. Daptomycin dose groups were not associated with survival in the adjusted model (Table 2).

Secondary outcomes

Daptomycin dose groups

There was no significant difference on univariate analysis between daptomycin dosing groups and the requirement for transfer to the ICU within 48 hours of the index blood culture ($P=0.696$), hospital length of stay ($P=0.982$), or development of adverse effects [CPK elevation ($P=0.632$), acute kidney injury ($P=0.165$) and eosinophilic pneumonia (no cases)] (Table 1). Microbiological failure was seen in 21 patients (18.9%) and this was significantly associated with daptomycin dose groups: 33.3% versus 12.1% versus 19.7% (low versus medium versus high dose, $P=0.036$). Notably, of these 21 patients, four (23.8%) experienced development of daptomycin resistance (MIC increased >8 mg/L) on at least one of the repeat blood cultures. Of these four patients, three were relapse infections (with two having an infection source of 'primary BSI' and a third with an intra-abdominal source), while the fourth patient had a persistent BSI that was associated with an intra-abdominal infection source.

Daptomycin versus teicoplanin in vanB *VRE*fm *BSIs*

Of the 144 *vanB* VRE*fm* BSIs (Figure 1), 80 were treated with teicoplanin definitive therapy compared with 64 with daptomycin. The *vanB* VRE*fm* populations were similar in all demographics except that males were more likely to be prescribed daptomycin definitive therapy (67.2% versus 48.8%, $P=0.029$; Table 3) and the time to first dose was more rapid in patients receiving daptomycin compared with teicoplanin definitive therapy (31.9 versus 46.1 hours, $P<0.001$, Table 3). There was no difference in crude 30-day in-hospital mortality between patients treated with daptomycin and teicoplanin definitive therapy (15.6% versus 17.5%, $P=0.825$; Table 3). There were also no differences in the requirement for transfer to ICU within 48 hours of the index positive blood culture (3.7% versus 5.6%, $P=0.698$), hospital length of stay (17.0 versus 19.0 days, $P=0.349$) and microbiological failure ($P=0.174$). The choice of daptomycin compared with teicoplanin was also not associated with survival in the adjusted model [AcsHR: 0.67 (95% CI: 0.28–1.59), Table S4].

Table 1. Baseline characteristics, microbiology and clinical outcomes, by daptomycin dose group, according to actual body weight

	Total $n=111$	Low (≤7.9 mg/kg) $n=12$	Medium (8–9.9 mg/kg) $n=33$	High (≥10 mg/kg) $n=66$	*P* value
Baseline demographics					
Age[a], years	63.0 (47.0, 70.0)	61.5 (39.0, 72.0)	62.0 (47.0, 68.0)	64.0 (50.0, 70.0)	0.479
Male	75 (67.6%)	8 (66.7%)	24 (72.7%)	43 (65.2%)	0.760
Weight[a], kg	74.0 (64.3–88.0)	69.3 (63.1–93.0)	74.0 (62.2–86.7)	75.2 (65.9–88.0)	0.998
BMI categories, kg/m^2					0.651
Underweight (<18.5)	9 (8.1%)	0 (0.0%)	5 (15.2%)	4 (6.1%)	
Normal (18.5–24.9)	35 (31.5%)	5 (41.7%)	9 (27.3%)	21 (31.8%)	
Overweight (25–29.9)	39 (35.1%)	3 (25.0%)	12 (36.4%)	24 (36.4%)	
Obese (≥30)	28 (25.2%)	4 (33.3%)	7 (21.2%)	17 (25.8%)	
ICU at time of positive blood culture	20 (18.0%)	1 (8.3%)	4 (12.1%)	15 (22.7%)	0.401
Diabetes	21 (18.9%)	3 (25.0%)	7 (21.2%)	11 (16.7%)	0.637
Liver cirrhosis	3 (2.7%)	1 (8.3%)	1 (3.0%)	1 (1.5%)	0.317
Creatinine[a], mcmol/L	67 (60.0, 105.0)	75 (63.0, 135.0)	68 (56.0, 103.0)	66 (60.0, 94.0)	0.289
eGFR (non-RRT patients), mL/min/1.73 m^2					0.252
>90	54 (55.7%)	5 (45.5%)	19 (63.3%)	30 (53.6%)	
30–90	38 (39.2%)	4 (36.4%)	11 (36.7%)	23 (41.1%)	
<30	5 (5.2%)	2 (18.2%)	0 (0.0%)	3 (5.4%)	
Renal replacement therapy (RRT)	14 (12.6%)	1 (8.3%)	3 (9.1%)	10 (15.2%)	0.762
Type of renal replacement therapy					1.00
CRRT	11/14 (78.6%)	1/1 (100.0%)	3/3 (100.0%)	7/10 (70.0%)	
Haemodialysis	2/14 (14.3%)	0/1 (0.0%)	0/3 (0.0%)	2/20 (20.0%)	
Peritoneal dialysis	1/14 (7.1%)	0/1 (0.0%)	0/3 (0.0%)	1/10 (10.0%)	
Malignant haematological condition	66 (59.5%)	6 (50.0%)	22 (66.7%)	38 (57.6%)	0.580
Stem cell transplant	25 (22.5%)	2 (16.7%)	6 (18.2%)	17 (25.8%)	0.706
Solid organ transplant	7 (6.3%)	1 (8.3%)	4 (12.1%)	2 (3.0%)	0.150
Neutrophil count, x10^9/L[a]	0.0 (0.0, 5.1)	1.5 (0.0, 4.7)	0.0 (0.0, 3.6)	0.0 (0.0, 5.4)	0.733
Neutropenia (count <0.5 x 10^9/L)	68 (61.3%)	6 (50.0%)	21 (63.6%)	41 (62.1%)	0.741
Hypoalbuminaemia (albumin ≤33 g/L)	106 (95.5%)	11 (91.7%)	32 (97.0%)	63 (95.5%)	0.626
Pitt Bacteraemia Score[a]	1.0 (0.0, 2.0)	0.5 (0.0, 1.0)	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.514
Source of VRE*fm* BSI					0.339
Primary BSI	47 (42.3%)	6 (50.0%)	12 (36.4%)	29 (43.9%)	
Line associated	32 (28.8%)	2 (16.7%)	9 (27.3%)	21 (31.8%)	
Intra-abdominal	23 (20.7%)	2 (16.7%)	10 (30.3%)	11 (16.7%)	
Other	7 (6.3%)	1 (8.3%)	1 (3.0%)	5 (7.6%)	
Urinary	2 (1.8%)	1 (8.3%)	1 (3.0%)	0 (0.0%)	
Antibiotic treatment					
Time to active antibiotic therapy[a], hours	35.9 (23.6, 46.1)	32.6 (19.7, 37.2)	33.5 (26.0, 43.8)	38.4 (23.3, 47.3)	0.330
Duration of VRE therapy[a], days	12.9 (10.4, 16.4)	13.6 (10.6, 19.9)	12.9 (11.4, 14.7)	13.0 (10.3, 16.4)	0.826
Daptomycin dose[a], mg/kg (actual body weight)	10.2 (9.6, 11.0)	7.2 (6.1, 7.8)	9.6 (9.1, 9.8)	10.9 (10.3, 11.7)	<0.001
Daptomycin dose[a], mg/kg (dosing weight)	10.6 (9.8, 11.9)	7.8 (6.4, 9.2)	9.8 (9.5, 10.0)	11.6 (10.5, 12.7)	<0.001
Input from the ID Unit	110 (99.1%)	12 (100.0%)	33 (100.0%)	65 (98.5%)	1.00
Statin therapy	17 (15.3%)	1 (8.3%)	4 (12.1%)	12 (18.2%)	0.676
Concurrent beta-lactam therapy	103 (92.8%)	11 (91.7%)	31 (93.9%)	61 (92.4%)	1.00
Treated as infective endocarditis	5 (4.5%)	0 (0.0%)	0 (0.0%)	5 (7.6%)	0.287
Dual VRE*fm* therapy	6 (5.4%)	2 (16.7%)	1 (3.0%)	3 (4.5%)	0.228
Microbiology					
Known VRE colonization	13 (11.7%)	0 (0.0%)	5 (15.2%)	8 (12.1%)	0.515
VRE*fm* genotype					0.475
vanA	44 (39.6%)	4 (33.3%)	17 (51.5%)	23 (34.8%)	
vanB	64 (57.7%)	8 (66.7%)	15 (45.5%)	41 (62.1%)	
vanA and *vanB*	3 (2.7%)	0 (0.0%)	1 (3.0%)	2 (3.0%)	

Continued

Table 1. *Continued*

	Total $n=111$	Low (≤7.9 mg/kg) $n=12$	Medium (8–9.9 mg/kg) $n=33$	High (≥10 mg/kg) $n=66$	*P* value
Daptomycin MIC[b]	109	12	31	66	0.401
≤1	11 (10.1%)	2 (16.7%)	3 (9.7%)	6 (9.1%)	
2	81 (74.3%)	8 (66.7%)	26 (83.9%)	47 (71.2%)	
4	17 (15.6%)	2 (16.7%)	2 (6.5%)	13 (19.7%)	
Time from admission to index blood culture[a], days	17.0 (13.0–24.0)	24.5 (14.0–30.5)	17.0 (15.0–24.0)	17.0 (10.0–22.0)	0.176
Polymicrobial index blood culture	10 (9.0%)	2 (16.7%)	3 (9.1%)	5 (7.6%)	0.549
Clinical outcomes					
30-day in-hospital mortality	19 (17.1%)	2 (16.7%)	3 (9.1%)	14 (21.2%)	0.363
Transfer to ICU within 48 hours[c]	3/91 (3.3%)	0/11 (0.0%)	0/29 (0.0%)	3/51 (5.9%)	0.696
Length of stay[a], days	18.0 (15.0, 34.0)	18.5 (13.5, 31.5)	18.0 (16.0, 31.0)	17.5 (15.0, 34.0)	0.982
Time to death[a], days	16.0 (13.0, 20.0)	21.0 (15.0, 27.0)	16.0 (16.0, 18.0)	14.5 (12.0, 20.0)	0.578
Microbiological failure					0.036
None	90 (81.1%)	8 (66.7%)	29 (87.9%)	53 (80.3%)	
Persistent	9 (8.1%)	0 (0.0%)	1 (3.0%)	8 (12.1%)	
Relapse	9 (8.1%)	2 (16.7%)	2 (6.1%)	5 (7.6%)	
Persistent plus relapse	3 (2.7%)	2 (16.7%)	1 (3.0%)	0 (0.0%)	
Daptomycin adverse effects					
Elevated CPK[d]	5/107 (4.7%)	1/12 (8.3%)	1/31 (3.2%)	3/51 (4.7%)	0.632
Acute kidney injury	11 (9.9%)	3 (25.0%)	2 (6.1%)	6 (9.1%)	0.165
Eosinophilic pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Values expressed as n (%).
[a]Data expressed as median (IQR).
[b]$n=2$ patients did not have MIC testing performed.
[c]$n=20$ patients already in ICU not included..
[d]$n=4$ patients did not have CPK measured.

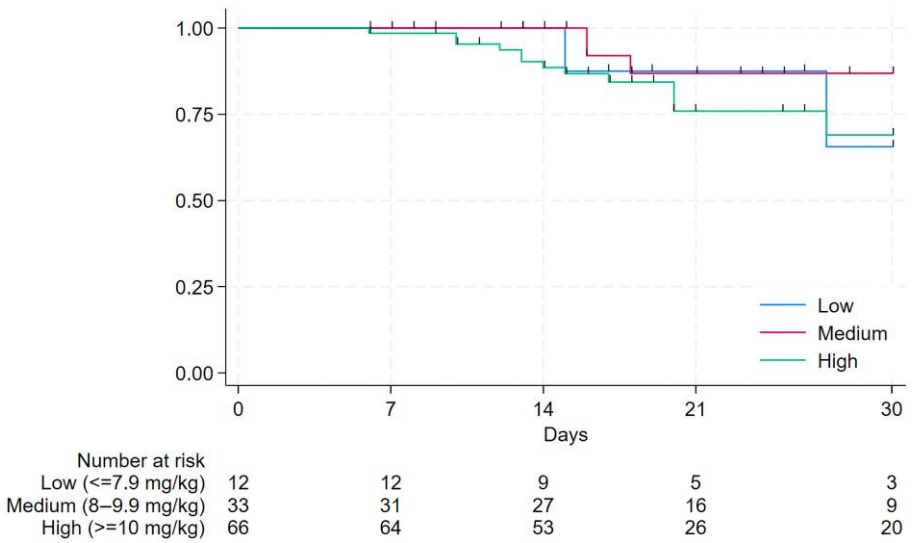

Figure 2. Kaplan–Meier survival curve for daptomycin dose groups using actual body weight ($n=111$, log rank $P=0.369$). Black ticks indicate where patients were discharged before 30 days.

Table 2. Association between baseline characteristics, microbiology and clinical outcomes with survival for VREfm BSIs treated with definitive daptomycin

	Total $n=111$	Alive $n=92$	Deceased $n=19$	*P* value	Unadjusted cause-specific hazard ratio (95% CI)	Adjusted cause-specific hazard ratio[e] (95% CI)
Dose groups						
Low (≤7.9 mg/kg)	12 (10.8%)	10 (10.9%)	2 (10.5%)	0.363	Reference	Reference
Medium (8–9.9 mg/kg)	33 (29.7%)	30 (32.6%)	3 (15.8%)		0.51 (0.08, 3.03)	0.66 (0.11, 4.04)
(≥10 mg/kg)	66 (59.5%)	52 (56.5%)	14 (73.7%)		1.20 (0.27, 5.29)	2.76 (0.58, 13.2)
Baseline demographics						
Age[a], years	63 (47.0–70.0)	64 (48.0–70.0)	59 (45.0–72.0)	0.652		
Male	75 (67.6%)	64 (69.6%)	11 (57.9%)	0.420		
Weight[a], kg	74.0 (64.0–88.0)	76.0 (66.0–90.0)	66.0 (60.0–80.0)	0.094		
BMI categories, kg/m^2						
Underweight (<18.5)	9 (8.1%)	7 (7.6%)	2 (10.5%)	0.110		
Healthy (18.5–24.9)	35 (31.5%)	28 (30.4%)	7 (36.8%)			
Overweight (25–29.9)	39 (35.1%)	30 (32.6%)	9 (47.4%)			
Obese (≥30)	28 (25.2%)	27 (29.3%)	1 (5.3%)			
ICU at time of positive blood culture	20 (18.0%)	10 (10.9%)	10 (52.6%)	<0.001		
Diabetes	21 (18.9%)	18 (19.6%)	3 (15.8%)	1.000		
Liver cirrhosis	3 (2.7%)	2 (2.2%)	1 (5.3%)	0.434		
Creatinine[a], mcmol/L	67 (60.0, 105.0)	67 (59.0, 103.0)	75 (65.0, 168.0)	0.108		
eGFR (non-RRT patients), mL/min/1.73 m^2						
>90	54 (55.7%)	48 (55.2%)	6 (60.0%)			
30–90	38 (39.2%)	36 (41.4%)	2 (20.0%)			
<30	5 (5.2%)	3 (3.4%)	2 (20.0%)	0.060		
Renal replacement therapy	14 (12.6%)	5 (5.4%)	9 (47.4%)	<0.001	5.83 (2.36, 14.4)	—
Type of renal replacement therapy						
CRRT	11/14 (78.6%)	3/5 (60.0%)	8/9 (88.9%)	0.440		
Haemodialysis	2/14 (14.3%)	1/5 (20.0%)	1/9 (11.1%)			
Peritoneal dialysis	1/14 (7.1%)	1/5 (20.0%)	0/9 (0.0%)			
Malignant haematological condition	66 (59.5%)	56 (60.9%)	10 (52.6%)	0.610		
Stem cell transplant	25 (22.5%)	21 (22.8%)	4 (21.1%)	1.000		
Solid organ transplant	7 (6.3%)	6 (6.5%)	1 (5.3%)	1.000		
Neutrophil count, x10^9/L[a]	0 (0–5)	0 (0–4)	1 (0–22)	0.029	1.11 (1.05, 1.17)	1.11 (1.03, 1.19)
Neutropenia (count <0.5 x 10^9/L)	68 (61.3%)	59 (64.1%)	9 (47.4%)	0.201		
Hypoalbuminaemia (albumin ≤33 g/L)	106 (95.5%)	89 (96.7%)	17 (89.5%)	0.202		
Pitt Bacteraemia Score[a]	1 (0.0–2.0)	1 (0.0–2.0)	3 (1.0–9.0)	<0.001	1.23 (1.09, 1.38)	1.00 (0.85, 1.17)
Source of VRE*fm* BSI						
Primary BSI	47 (42.3%)	38 (41.3%)	9 (47.4%)	0.985		
Line associated	32 (28.8%)	27 (29.3%)	5 (26.3%)			
Intra-abdominal	23 (20.7%)	19 (20.7%)	4 (21.1%)			
Other	7 (6.3%)	6 (6.5%)	1 (5.3%)			
Urinary	2 (1.8%)	2 (2.2%)	0 (0.0%)			
Antibiotic treatment						
Time to active antibiotic therapy[a], hours	35.9 (23.6, 46.1)	37.2 (25.8, 47.2)	24.4 (18.5, 44.5)	0.031	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)
Duration of VRE therapy[a], days	12.9 (10.4, 16.4)	13.0 (11.9, 16.5)	12.0 (8.0, 16.3)	0.273		
Daptomycin dose[a], mg/kg (actual body weight)	10.2 (9.6, 11.0)	10.1 (9.5, 10.9)	10.6 (10.0, 11.4)	0.149		
Daptomycin dose[a], mg/kg (dosing weight)	10.6 (9.8, 11.9)	10.5 (9.7, 11.9)	10.6 (10.0, 11.6)	0.953		
Input from the ID Unit	110 (99.1%)	92 (100.0%)	18 (94.7%)	0.171		
Statin therapy	17 (15.3%)	14 (15.2%)	3 (15.8%)	1.000		
Concurrent beta-lactam therapy	103 (92.8%)	84 (91.3%)	19 (100.0%)	0.347		
Treated as infective endocarditis	5 (4.5%)	4 (4.3%)	1 (5.3%)	1.000		

Continued

Table 2. *Continued*

	Total $n=111$	Alive $n=92$	Deceased $n=19$	*P* value	Unadjusted cause-specific hazard ratio (95% CI)	Adjusted cause-specific hazard ratio[e] (95% CI)
Dual VRE*fm* therapy	6 (5.4%)	5 (5.4%)	1 (5.3%)	1.000		
Microbiology						
Known VRE colonization	13 (11.7%)	10 (10.9%)	3 (15.8%)	0.694		
VRE*fm* genotype				0.534		
vanA	44 (39.6%)	36 (39.1%)	8 (42.1%)			
vanB	64 (57.7%)	54 (58.7%)	10 (52.6%)			
vanA and *vanB*	3 (2.7%)	2 (2.2%)	1 (5.3%)			
Daptomycin MIC[b]	109	90	19	0.638		
≤1	11 (10.1%)	10 (11.1%)	1 (5.3%)			
2	81 (74.3%)	67 (74.4%)	14 (73.7%)			
4	17 (15.6%)	13 (14.4%)	4 (21.1%)			
Time from admission to index blood culture[a], days	17.0 (13.0, 24.0)	17.5 (13.0, 24.0)	17.0 (10.0, 29.0)	0.644		
Polymicrobial index blood culture	10 (9.0%)	9 (9.8%)	1 (5.3%)	1.000		
Clinical outcomes						
Transfer to ICU within 48 hours[c]	3/91 (3.3%)	1/82 (1.2%)	2/9 (22.2%)	0.025		
Length of stay[a], days	18.0 (15.0, 34.0)	19.0 (15.0, 38.0)	16.0 (13.0, 20.0)	0.027		
Time to death[a], days	16.0 (13.0, 20.0)	—	16.0 (13.0, 20.0)			
Microbiological failure				0.122		
None	90 (81.1%)	77 (83.7%)	13 (68.4%)			
Persistent	9 (8.1%)	5 (5.4%)	4 (21.1%)			
Relapse	9 (8.1%)	7 (7.6%)	2 (10.5%)			
Persistent plus relapse	3 (2.7%)	3 (3.3%)	0 (0.0%)			
Daptomycin adverse effects						
Elevated CPK[d]	5/107 (4.7%)	2/88 (2.3%)	3/19 (15.8%)	0.038	4.87 (1.37,17.3)	—
Acute kidney injury	11 (9.9%)	6 (6.5%)	5 (26.3%)	0.021	3.06 (1.10, 8.52)	7.33 (2.03, 26.5)
Eosinophilic pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	—		

P values calculated using Fisher's exact or Mann–Whitney *U*-test. Cause-specific hazard ratios from Cox regression analysis with 30-day in-hospital mortality as dependent variable and dose groups as main covariate of interest. Values expressed as *n* (%).

[a]Data expressed as median (IQR).

[b]$n=2$ patients did not have MIC testing performed.

[c]$n=20$ patients already in ICU not included.

[d]$n=4$ patients did not have CPK measured.

[e]Multivariable model was adjusted for severity of illness (Pitt Bacteraemia Score), and initially considered all variables that were $P<0.05$ on univariate analysis [renal replacement therapy, neutrophil count, timely administration of daptomycin therapy, elevation in CPK and development of acute kidney injury (from any cause)]. Although location in ICU at the time of index positive blood culture and transfer to ICU within 48 hours were also significant in the univariate analysis, they were correlated with Pitt Bacteraemia Score and therefore not included in the multivariable model. To avoid overfitting (due to small numbers), final model retained only those variables that remained significant at $P<0.05$ (neutrophil count, timely administration of daptomycin therapy and development of acute kidney injury (from any cause)).

Daptomycin adverse events (daptomycin cohort, n = *111 patients)*

No cases of eosinophilic pneumonia were suspected or confirmed, while 11 (9.9%) patients experienced an acute kidney injury (all-cause) during daptomycin therapy. Of the 107 patients who had CPK monitored at least once during daptomycin therapy, an elevation occurred in five patients (4.7%), with three mild and two major cases. Of those with CPK elevation, four patients had renal impairment on the day of the index blood culture being drawn (including two patients receiving CRRT), while a single patient had no documented renal impairment. Seventeen patients (15.3%) received at least one dose of a concomitant statin during their daptomycin therapy, none of whom experienced CPK elevation.

Discussion

In this study of 111 patients receiving definitive daptomycin therapy for the treatment of a first episode VRE*fm* BSI, we found no difference in 30-day in-hospital mortality when daptomycin was categorized into low, medium or high dosing groups,

Table 3. Baseline characteristics, microbiology and clinical outcomes for patients with vanB VREfm BSIs ($n=144$), by treatment

	Total $n=144$	Teicoplanin $n=80$	Daptomycin $n=64$	*P* value
Baseline demographics				
Age[a], years	64.0 (52.0, 71.0)	64.0 (53.5, 71.5)	65.0 (51.0, 70.5)	0.839
Male	82 (56.9%)	39 (48.8%)	43 (67.2%)	0.029
Weight[a], kg	74.8 (62.2, 88.2)	74.5 (57.2, 86.2)	76.9 (64.4, 90.2)	0.192
BMI categories, kg/m^2				0.256
Underweight (<18.5)	12 (8.3%)	6 (7.5%)	6 (9.4%)	
Healthy (18.5–24.9)	46 (31.9%)	31 (38.8%)	15 (23.4%)	
Overweight (25–29.9)	48 (33.3%)	23 (28.7%)	25 (39.1%)	
Obese (≥30)	38 (26.4%)	20 (25.0%)	18 (28.1%)	
ICU at time of positive blood culture	19 (13.2%)	9 (11.2%)	10 (15.6%)	0.467
Diabetes	24 (16.7%)	13 (16.2%)	11 (17.2%)	1.000
Liver cirrhosis	6 (4.2%)	3 (3.8%)	3 (4.7%)	1.000
Creatinine[a], mcmol/L	67.0 (59.0, 92.0)	67.0 (55.0, 86.0)	70.0 (60.0, 108.0)	0.139
eGFR (non-RRT patients), mL/min/1.73 m^2				0.589
>90	71 (54.6%)	44 (58.7%)	27 (49.1%)	
30–90	53 (40.8%)	28 (37.3%)	25 (45.5%)	
<30	6 (4.6%)	3 (4.0%)	3 (5.5%)	
Renal replacement therapy	14 (9.7%)	5 (6.2%)	9 (14.1%)	0.158
Type of renal replacement therapy				1.00
CRRT	10 (71.0%)	4 (80.0%)	6 (67.0%)	
Haemodialysis	3 (21.0%)	1 (20.0%)	2 (22.0%)	
Peritoneal dialysis	1 (7.0%)	0 (0.0%)	1 (11.0%)	
Malignant haematological condition	84 (58.3%)	48 (60.0%)	36 (56.2%)	0.734
Stem cell transplant	34 (23.6%)	14 (17.5%)	20 (31.2%)	0.075
Solid organ transplant	4 (2.8%)	4 (5.0%)	0 (0.0%)	0.129
Neutrophil count, x10^9/L[a]	0.0 (0.0, 6.5)	0.0 (0.0, 7.6)	0.0 (0.0, 5.6)	0.346
Neutropenia (count <0.5 x 10^9/L)	90 (62.5%)	50 (62.5%)	40 (62.5%)	1.00
Hypoalbuminaemia (albumin ≤33, g/L)	138 (95.8%)	77 (96.2%)	61 (95.3%)	1.000
Pitt Bacteraemia Score[a]	1.0 (0.0, 2.0)	0.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.050
Source of VRE*fm* BSI				0.672
Primary BSI	58 (40.3%)	28 (35.0%)	30 (46.9%)	
Line associated	36 (25.0%)	21 (26.2%)	15 (23.4%)	
Intra-abdominal	33 (22.9%)	21 (26.2%)	12 (18.8%)	
Other	14 (9.7%)	8 (10.0%)	6 (9.4%)	
Urinary	3 (2.1%)	2 (2.5%)	1 (1.6%)	
Antibiotic treatment				
Time to active antibiotic therapy[a], hours	38.6 (25.8, 51.9)	46.1 (30.2, 59.1)	31.9 (23.5, 42.4)	<0.001
Duration of VRE*fm* therapy[a], days	13.0 (10.6, 16.9)	13.4 (10.6, 18.2)	12.9 (10.6, 14.6)	0.210
Daptomycin dose[a], mg/kg (actual body weight)	10.4 (9.2, 11.3)	—	10.4 (9.2, 11.3)	—
Daptomycin dose[a], mg/kg (dosing weight)	11.1 (9.6, 12.3)	—	11.1 (9.6, 12.3)	—
Teicoplanin dose[a], mg/kg (actual body weight)	10.2 (9.1, 11.3)	10.2 (9.1, 11.3)	—	—
Teicoplanin dose[a], mg/kg (dosing weight)	10.6 (9.3, 12.7)	10.6 (9.3, 12.7)	—	—
Input from the ID Unit	141 (97.9%)	77 (96.2%)	64 (100.0%)	0.254
Treated as infective endocarditis	6 (4.2%)	4 (5.0%)	2 (3.1%)	0.693
Dual VRE*fm* therapy	3 (2.1%)	0 (0.0%)	3 (4.7%)	0.085
Microbiology				
Known VRE colonization	16 (11.1%)	10 (12.5%)	6 (9.4%)	0.604
Daptomycin MIC[c]	137	74	63	0.017
≤1	13 (9.5%)	4 (5.4%)	9 (14.3%)	
2	92 (67.2%)	46 (62.2%)	46 (73.0%)	
4	29 (21.2%)	21 (28.4%)	8 (12.7%)	
8+	3 (2.2%)	3 (4.1%)	0 (0.0%)	

Continued

Table 3. *Continued*

	Total $n=144$	Teicoplanin $n=80$	Daptomycin $n=64$	*P* value
Time from admission to index blood culture[a], days	16.0 (10.0, 22.0)	14.5 (8.0, 21.0)	17.0 (12.0, 23.0)	0.078
Polymicrobial index blood culture	14 (9.7%)	6 (7.5%)	8 (12.5%)	0.399
Clinical outcomes				
30-day in-hospital mortality	24 (16.7%)	14 (17.5%)	10 (15.6%)	0.825
Transfer to ICU within 48 hours[b]	6/125 (4.8%)	4/71 (5.6%)	2/54 (3.7%)	0.698
Length of stay[a], days	18.0 (14.0, 29.0)	19.0 (15.0, 29.0)	17.0 (14.0, 29.5)	0.349
Time to death[a], days	14.0 (10.5, 17.0)	14.0 (10.0, 18.0)	14.5 (12.0, 16.0)	0.977
Microbiological failure				0.174
None	122 (84.7%)	67 (83.8%)	55 (85.9%)	
Persistent	10 (6.9%)	8 (10.0%)	2 (3.1%)	
Relapse	10 (6.9%)	5 (6.2%)	5 (7.8%)	
Persistent plus relapse	2 (1.4%)	0 (0.0%)	2 (3.1%)	

P values calculated using Fisher's exact or Mann–Whitney *U*-test. Values expressed as *n* (%).
[a]Data expressed as median (IQR).
[b]$n=19$ patients already in ICU not included.
[c]$n=7$ patients did not have MIC testing performed.

however, daptomycin dose groups were associated with microbiological failure. Overall, in-hospital mortality was low (17.1%), in comparison to other contemporary reports. We also observed no difference in mortality in patients with *vanB* VRE*fm* BSI who were treated with definitive daptomycin or teicoplanin.

The findings from our study differs from other published work. Britt *et al*. reported on 911 patients with predominantly VRE*fm* BSI and showed that 30-day mortality was significantly lower among patients who received high-dose daptomycin (≥10 mg/kg) compared with other dosing strategies (risk ratio, 0.83; 95% CI, 0.74 to 0.94; $P=0.015$).[3] Two studies by Chuang *et al*. demonstrated similar findings with either ≥9 mg/kg[4] or ≥11 mg/kg[6] showing a mortality benefit. Potential reasons for the different findings with our study is the distribution of milligram per kilogram daptomycin doses and the low overall mortality. Most patients in our study received higher doses [59.5% received ≥10 mg/kg, the median dose was 10.2 mg/kg (IQR: 9.6 to 11.0 mg/kg)]. Most (77.8%) patients in Britt *et al*. were treated with standard dose daptomycin (6 ± 0.5 mg/kg), with only 6.6% receiving a high dose (>10 mg/kg).[3] Chuang *et al*. reported 22.3% of patients received daptomycin doses ≥9 mg/kg in their 2017 study, while only 19.5% of patients received ≥11 mg/kg in their 2022 study.[4,6] Within our cohort, 25.2% of patients had a BMI ≥30 kg/m^2, which is less than the 36.8% reported by Britt *et al*. Within our institution, daptomycin is dosed according to the BMI-based dosing weight, where adjusted body weight daptomycin dosing is used for patients with a BMI ≥30 kg/m^2. The use of actual body weight to guide daptomycin dosing for patients classified as obese has been associated with increased risk of CPK elevation and subsequent drug discontinuation compared with non-obese patients,[13] while the use of adjusted body weight dosing has shown no outcome differences when compared with actual body weight dosing.[14] When we analysed our data using dosing weight for daptomycin dose groups, again we found no difference in 30-day mortality between high, medium and low dose groups. Given the small numbers of patients in our cohort receiving low and medium daptomycin doses compared with the comparator studies, our study may have been underpowered to detect a difference in mortality. We note there is international interest in the application of fixed dose daptomycin for the treatment of Gram-positive infections, rather than milligram per kilogram dosing regimens used in our study.[15] Further work is warranted before applying a fixed dose strategy to VRE*fm* patient populations.

In our daptomycin definitive treatment population, overall 30-day in-hospital mortality was 17.1%, which is lower than the 2023 Australian national all-cause mortality at 30 days of 28.7% for VRE*fm* BSIs.[7] Chuang *et al*. reported a 14-day mortality rate of 35.7% in patients receiving daptomycin ≥6 mg/kg, while a subgroup of patients dosed at 8.2 to 12.2 mg/kg were associated with the lowest mortality of 18.5%[4] In their second cohort, Chuang *et al*. identified a 28-day mortality rate of 45.1% in patients receiving ≥8 mg/kg, with the odds of mortality due to VRE BSI decreasing by 15% with each mg/kg increase in the daptomycin dose (aOR = 0.85; 95% CI = 0.73–0.99; $P=0.03$).[6] The higher mortality rate observed in these studies may reflect immortal time bias as they included all patients with VRE BSI irrespective of treatment duration received. Despite this, Britt *et al*. reported an overall high mortality of 29.9% in patients receiving treatment for ≥48 hours, which was reduced to 16.7% when patients were treated with daptomycin doses ≥10 mg/kg.[3] Severity of illness is an important confounder for mortality. Our cohort had a median Pitt Bacteraemia Score of 1.0 (IQR: 0.0 to 2.0) however, there was no statistically significant difference between daptomycin dosing groups. Even with adjustment for severity of illness, we still did not observe any differences in mortality between the daptomycin dosing groups.

The overall rates of persistent, relapse and both persistent plus relapse BSIs in our study (8.1%, 8.1% and 2.7%, respectively) was slightly higher than that observed in other studies. There was an

association between microbiological failure and daptomycin dose groups ($P=0.036$), suggesting that patients in the low dose group had a higher proportion of relapse and persistent plus relapse BSIs compared with medium and high-dose groups. Britt *et al*. reported low rates of 60-day VRE*fm* BSI recurrence, with 2.9%, 2.6% and 2.4% in the standard, medium and high daptomycin dosing groups, respectively, with no difference in recurrence observed between the different daptomycin dosing groups ($P=0.976$).[3] Chuang *et al*. used a composite endpoint of 'microbiological failure' that incorporated re-isolation of VRE in blood cultures and early mortality (≤7 day) and showed that daptomycin doses ≥11 mg/kg had lower rates than doses of <9 mg/kg and 9 to <11 mg/kg ($P=0.05$).[6] While direct comparison of the results between these studies is difficult, we support the notion proposed by Britt *et al*. that early microbiological clearance may be a key reason for improved survival in VRE*fm* BSIs. Our study specifically focused on daptomycin dosing within the first 96 hours following the index blood culture, given the importance of clearing blood cultures in the first few days. It was beyond the scope of our study to investigate the impact of other management interventions (e.g. removal of infected intravenous lines) on the rates of persistent and relapsed BSIs.

A unique aspect to our patient cohort is the predominance of the *vanB* VRE*fm* genotype. *vanB* infections predominate in Australia and there is a paucity of studies comparing antibiotic treatment approaches for *vanB* VRE*fm* BSIs. We did not observe a difference in 30-day in-hospital mortality between patients receiving daptomycin and teicoplanin definitive therapy for the treatment of *vanB* VRE*fm* BSI [AcsHR 0.67 (95% CI: 0.28–1.59)]. The lack of published literature on the role of daptomycin specifically for the treatment of *vanB* VRE*fm* infections probably reflects the predominance of the *vanA* genotype in larger developed countries, rather than a concern specifically relating to efficacy. The literature supporting treatment of *vanB* VRE BSIs is relatively limited and includes two Australian retrospective studies that used teicoplanin treatment.[16,17] Xie *et al*. postulated that clinicians may preferentially administer daptomycin instead of teicoplanin for sicker patients,[16] with our study supporting this. Patients receiving daptomycin had a higher median Pitt Bacteraemia Score (1.0 versus 0.0, $P=0.05$).

Despite the use of higher daptomycin doses, we did not observe any safety concerns in patients receiving at least one dose of daptomycin during the study period. In particular, higher daptomycin doses carry a concern for increased risk of skeletal muscle toxicity reflected through CPK elevation.[6,18] Our findings support those of Britt *et al*. and Chuang *et al*. that there was no observed association between high-dose daptomycin compared with lower dose groups ($P=0.632$).[3,4]

Our study is not without its limitations. This study was a retrospective review undertaken in a single institution and there are probably unexplained factors contributing to some of the findings (e.g. the inverse relationship between neutrophils and timely administration of daptomycin and 30-day mortality). Our institution has had evidence based daptomycin prescribing guidelines in place for the duration of the study. As such, we saw higher doses of daptomycin prescribed than reported elsewhere and this has probably limited the ability to detect a difference between the daptomycin dosing categories. The numbers of patients included in this study was relatively small compared with other published work,[3,6] and this probably affected the power to detect a significant difference between daptomycin dose groups. The predominance of *vanB* VRE*fm* isolates limits the generalisability of our findings to some international settings. Our institution experienced a local outbreak of *vanA* infections between 2019 and 2022 that resulted in a change in empiric prescribing for VRE*fm* BSIs from teicoplanin to daptomycin. This change to empiric daptomycin for VRE*fm* infections has been sustained since this time. Given the availability of teicoplanin in Australia, and a predominant *vanB* genotype, it is common for patients to receive more than one class of VRE active therapy during their treatment course (sequential therapy). Our consensus definition of definitive therapy focused on the first 3 days of active antibiotic therapy in the management and clearance of positive blood cultures and we acknowledge that some patients may have been too unwell to complete three days of therapy, while in other patients, antibiotic changes may have occurred after the first 3 days of treatment (e.g. daptomycin de-escalation to teicoplanin for *vanB* VRE*fm* BSIs). The incorporation of daptomycin concentration monitoring was beyond the scope of this study, however, may be considered in the future.

Conclusions

In a VRE*fm* BSI cohort where most patients received optimized daptomycin dosing against predominantly *vanB* VRE*fm*, we observed no association between daptomycin dose and 30-day in-hospital mortality. Despite the absence of an association between daptomycin dose group and all-cause 30-day in-hospital mortality, this study does support the ongoing use of daptomycin for the treatment of VRE*fm* BSIs. Given our low in-hospital 30-day mortality, and the demonstrated tolerability of daptomycin, we continue to support the use of doses ≥10 mg/kg when treating VRE*fm* BSIs with both the *vanA* and *vanB* genotypes. We also found no difference in mortality between patients with *vanB* VRE*fm* BSIs treated with definitive daptomycin or teicoplanin.

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This study was carried out as part of our routine work.

Transparency declaration

Iain Abbott has undertaken advisory board consultancy for Merck Sharp & Dohme (Australia) (June 2021) and GSK (November 2023), and invited speaker for Becton Dickinson (February 2025); Anton Peleg has received an investigator-initiated research grant from Merck Sharp & Dohme unrelated to the current project. All other authors have nothing to declare.

Supplementary data

Supplementary Tables S1–S4 are available as Supplementary data at *JAC-AMR* Online.

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