BRIEF REPORT

A Pharmacovigilance Analysis of Daptomycin Use Based on CLSI Susceptible Dose-Dependent Category

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ABSTRACT

Introduction: Daptomycin doses 8–12 mg/kg are recommended for susceptible dose-dependent *Enterococcus* species. However, data remain limited on safety outcomes of such dosing, compared to standard 4–6 mg/kg dosing.

Methods: In this retrospective cohort study, patients were stratified into daptomycin standard-dose ($\leq$ 6.5 mg/kg) versus high-dose ($\geq$ 7.5 mg/kg) groups. The primary outcome was daptomycin safety based on a composite of creatine kinase elevation, daptomycin-related peripheral blood eosinophilia, eosinophilic pneumonitis, alanine aminotransferase elevation, and alkaline phosphatase elevation. A secondary aim was to identify risk factors for daptomycin adverse effects. Inclusion criteria were age $\geq$ 18 years old, daptomycin receipt for $\geq$ 48 h, and *Enterococcus* cultures with a daptomycin minimal inhibitory concentration 2–4 mg/L.

Results: A total of 119 patients were included for analysis. Median daptomycin doses were 6.0 mg/kg (IQR 5.4, 6.1) and 8.1 mg/kg (IQR 7.9, 9.6) in the standard- and high-dose cohorts, respectively. Median durations were 13.5 days (standard-dose) and 16 days (high-dose) ($p = 0.02$). The composite safety endpoint occurred in 32.0% of the standard-dose group and 32.5% of the high-dose group ($p = 0.96$). Daptomycin was dose-reduced or held in 8.1% of patients experiencing an adverse effect. Concurrent antihistamine usage was associated

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with the composite outcome; however, there was no association with daptomycin dose or concurrent statin use.

Conclusion: High-dose daptomycin was not associated with increased laboratory abnormalities or adverse drug reactions compared to standard-dose daptomycin.

Keywords: Daptomycin; *Enterococcus*; Pharmacovigilance; Susceptible dose-dependent

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Key Summary Points

Daptomycin doses 8–12 mg/kg are recommended by the Clinical and Laboratory Standards Institute for susceptible dose-dependent (SDD) *Enterococcus* species.

However, data remain limited regarding safety outcomes of SDD dosing, compared to the standard 4–6 mg/kg dosing approved by the US Food and Drug Administration.

This retrospective cohort study compared safety outcomes of high-dose versus standard-dose daptomycin for enterococcal infections.

High-dose daptomycin was not associated with increased laboratory abnormalities or adverse drug reactions compared to standard-dose daptomycin.

Coupled with previous literature demonstrating daptomycin's dose-dependent efficacy, these findings support the use of SDD daptomycin dosing.

INTRODUCTION

Since January 2019, the Clinical and Laboratory Standards Institute has issued multiple revisions to daptomycin breakpoints in *Enterococcus* spp., specifically creating a susceptible dose-dependent (SDD) category (Supplemental Table 1). Under this guidance, SDD *Enterococcus* isolates

should be treated with daptomycin 8–12 mg/kg, compared to the standard dosage of 4–6 mg/kg used for fully susceptible isolates [1, 2]. This change was in response to literature demonstrating superior efficacy outcomes with higher doses of daptomycin [3–6]. However, data remains limited regarding the safety outcomes of daptomycin doses $\geq$ 8 mg/kg compared to 4–6 mg/kg in enterococcal infections. Existing literature is inconsistent, with several studies detecting dose-dependent toxicity, several detecting no difference, and many failing to assess this endpoint [6–9].

We performed a 2-year retrospective cohort study to compare the clinical outcomes of daptomycin $\geq$ 7.5 mg/kg (high dose) versus $\leq$ 6.5 mg/kg (standard dose) for enterococcal infections. The primary outcome was patient safety based on a composite endpoint of elevated creatine kinase (CK), daptomycin-related peripheral blood eosinophilia, eosinophilic pneumonitis, elevated alanine aminotransferase (ALT), and elevated alkaline phosphatase (ALP). A secondary aim was to identify risk factors for daptomycin adverse effects. We hypothesized there would be no difference in adverse drug reaction (ADR) rates between standard- and high-dose daptomycin.

METHODS

Ethics

This study was deemed to be exempt by the Mayo Clinic Institutional Review Board (approval number Mod20-011769-02) and was conducted in accordance with the Declaration of Helsinki and national and institutional standards. Informed consent was waived because of the retrospective nature of the study. The analysis used anonymized clinical data.

Study Setting, Design, and Population

This was a retrospective cohort study conducted at the Mayo Clinic Hospital in Rochester, MN. Data were collected from the electronic health record across two 1-year periods (May 1, 2017 to

May 1, 2018 and September 1, 2019 to September 1, 2020). These time periods correlated with an implementation of SDD reporting that resulted in median daptomycin doses increasing from 6.4 to 8.5 mg/kg, with a washout period in between. To allow for adjustments in dose rounding, patients in the standard-dose group were defined as those who received an average daptomycin dose of ≤ 6.5 mg/kg based on adjusted body weight (AdjBW), as per our usual institutional practice. Patients in the high-dose group were defined as those who received an average daptomycin dose of ≥ 7.5 mg/kg based on AdjBW.

Patients who met the following criteria were included: age ≥ 18 years, Minnesota research authorization, *Enterococcus* cultured from sterile sources or vancomycin-resistant *Enterococcus* (VRE) from urine with a daptomycin MIC of 2 or 4 mg/L, and inpatient or outpatient treatment with daptomycin for ≥ 48 h. For patients with multiple eligible encounters for the same infection, only the first encounter was included. Patients were excluded if they had an enterococcal pulmonary infection or were pregnant or incarcerated.

Microbiologic Methods and Data Collection

A microbiology report identifying patients with an *Enterococcus* spp. isolate with daptomycin susceptibilities within the study time frame was reviewed for inclusion and exclusion criteria. Organisms were identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI–TOF MS) using the Bruker MALDI–TOF MS system (Bruker Daltonics, Inc., Billerica, MA, USA). Daptomycin testing was performed using gradient diffusion testing (Etest, bioMérieux, Marcy l'Etoile, France).

Data were manually collected via chart review on patients who met study criteria. Potential cases of liver injury were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) and Roussel Uclaf Causality Assessment Method (RUCAM) causality scoring. Data were stored in a Research Electronic Data Capture (REDCap) database.

Outcomes and Clinical Definitions

The primary outcome was a composite safety endpoint of the occurrence of specific ADRs or laboratory abnormalities that might be daptomycin-mediated: CK elevation, peripheral blood eosinophilia, acute eosinophilic pneumonitis, ALT elevation, and/or ALP elevation. All values were assessed from the time of daptomycin initiation to 3 days after daptomycin discontinuation. Patients were considered not to have met the composite endpoint if they had documented measurement of at least one ADR parameter and did not have an ADR based on the following definitions. Creatinine kinase, ALT, and ALP elevations were defined as values at least three times the upper limit of normal, based on our institution's reference values (CK: 39–308 units/liter [U/L] for men, 26–192 U/L for women; ALT: 7–55 U/L for men, 7–45 U/L for women; ALP: 40–129 U/L for men, 35–104 U/L for women). Peripheral blood eosinophilia was defined as an eosinophil count > 1% of the total white blood cell count. Daptomycin-related peripheral blood eosinophilia was defined as an eosinophil count ≥ 5% of the total white blood cell count on two consecutive blood draws [10]. Daptomycin-induced eosinophilic pneumonitis was categorized as definite, probable, or unlikely, using criteria previously defined in the literature. Definite cases were those that met all the following criteria: concurrent exposure to daptomycin, fever, dyspnea with increased oxygen requirement or requiring mechanical ventilation, new infiltrates on chest radiograph X-ray or computed tomography (CT) scan, bronchoalveolar lavage (BAL) with > 25% eosinophils, and clinical improvement following daptomycin withdrawal. Probable cases were those that met all the following criteria: concurrent exposure to daptomycin, dyspnea with increased oxygen requirement or requiring mechanical ventilation, new infiltrates on chest X-ray or CT scan, BAL with > 25% eosinophils OR peripheral eosinophilia, and clinical improvement following daptomycin withdrawal. Unlikely cases were all other cases that did not meet the criteria for other categories [11].

Statistical Analysis

Data were summarized using means and standard deviations or medians and interquartile ranges for continuous data, and frequencies and percentages for categorical data. Baseline characteristics were compared between dosing groups using either *t* tests or Wilcoxon rank sum tests for continuous data and chi-square or Fisher's exact tests for categorical data. Logistic regression was used to assess the association between dosing group and having any safety-related outcome both univariately and after adjusting for other factors in a multivariable model. The variables in the multivariable model were selected using stepwise selection, forcing dosing group in the model. *p* values ≤ 0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 software (SAS Institute, Inc.; Cary, NC, USA).

RESULTS

A total of 119 patients had enterococcal isolates that met inclusion criteria; 75.6% (90/119) were identified as *Enterococcus faecium*, 20.2% (24/119) were identified as non-*faecium* species (18/119 *Enterococcus faecalis*, 5/119 *Enterococcus gallinarum*, 1/119 *Enterococcus hirae*), and 4.2% (5/119) were only identified to the genus level (Fig. 1). There were 76 (64%) patients included in the standard-dose group and 43 (36%) patients in the high-dose group. Baseline characteristics are summarized in Table 1. The mean patient age was 60.7 years, and the median weight was 76.1 kg. There were no significant between-group differences in baseline serum creatine (SCr), CK, or liver function tests (LFTs). Median daptomycin doses, based on AdjBW, were 6.0 mg/kg (IQR 5.4, 6.1; median dose 410 mg) in the standard-dose cohort, compared to 8.1 mg/kg (IQR 7.9, 9.6; median dose 580 mg) in the high-dose cohort. Median durations were 13.5 days (IQR 7, 23) in the standard-dose cohort and 16 days (IQR 10, 44) in the high-dose cohort (*p* = 0.02). There were statistically significant differences in daptomycin dosing frequency between the standard- and high-dose cohorts.

The composite endpoint occurred in 37 patients (32.2%), including 24/76 (32.0%) of the standard-dose group and 13/43 (32.5%) of the high-dose group (*p* = 0.96) (Table 2). There were no significant between-group differences in the incidence of any individual ADR, though there was a significant difference in time to onset of ALT elevation, occurring at a median of 1 day in the standard-dose cohort versus 31 days in the high-dose cohort (*p* = 0.004) (time to event curves, Supplementary Fig. 1). Within the total population, the most common event was liver function test (LFT) elevation (ALP elevation 21/84 [25.0%], ALT elevation 14/94 [14.9%]). On the basis of the NCI CTCAE Version 5.0, there were no between-group differences in the severity of hepatotoxicity [12]. RUCAM causality scoring revealed that of the 25 patients who experienced LFT elevations, daptomycin was considered to be unrelated in 19 cases (did not qualify for scoring per RUCAM criteria), excluded as a cause in 2 cases (RUCAM score ≤ 0), and an unlikely cause in 4 cases (RUCAM score 1–2) [13]. The second most common event was daptomycin-related peripheral eosinophilia, occurring in 16.5% (15/91) of the total population; however, there were no incidents of eosinophilic pneumonitis. The incidence of CK elevation was rare, at only 2.9% (3/104) of the total cohort. Of the three cases of CK elevation, two were asymptomatic and one was associated with upper extremity pain.

Despite a relatively high rate of laboratory abnormalities, there were only three cases (8.1% of patients experiencing the composite endpoint) in which daptomycin was dose-reduced or temporarily held: two cases with asymptomatic CK elevations and one case with symptomatic CK elevation (upper extremity pain), ALT elevation, and ALP elevation. There were no cases in which daptomycin was permanently discontinued as a result of an ADR.

Daptomycin dose was not associated with an increased risk of the composite outcome on multivariable analysis (*p* = 0.81), nor was concurrent statin administration on univariate analysis (*p* = 0.45). On multivariable analysis, factors associated with ADR occurrence included concurrent usage of an antihistamine (OR 3.24, 95% CI 1.16–9.02, *p* = 0.025) or
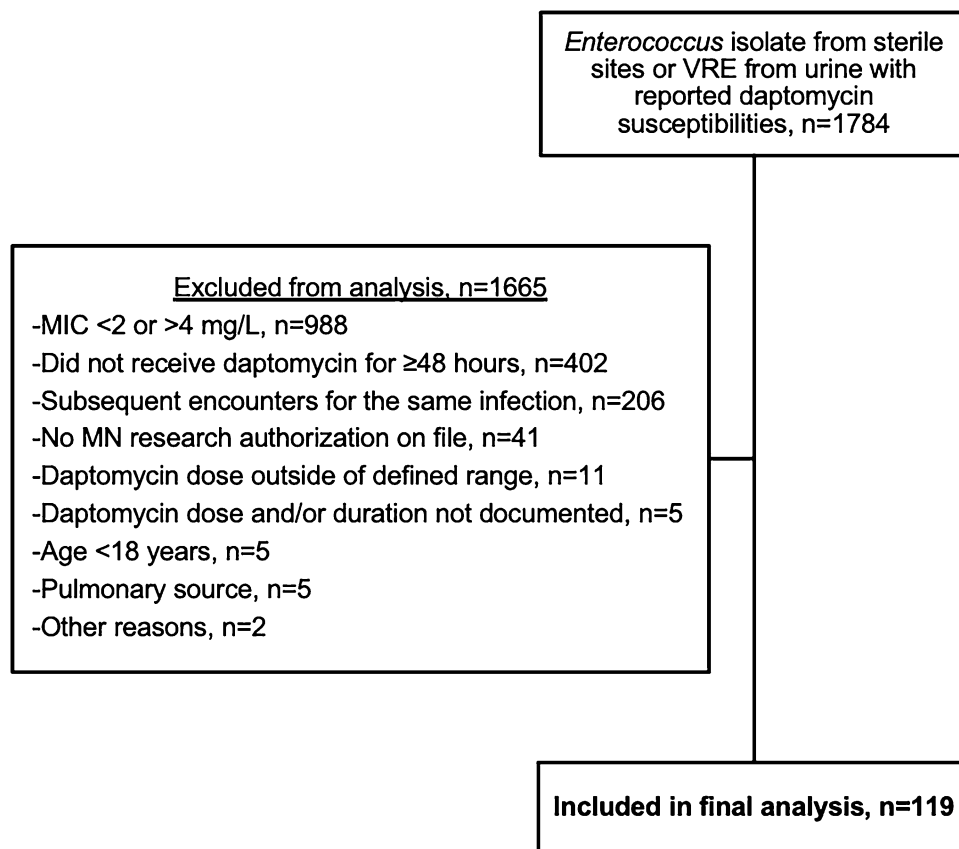
Fig. 1 Application of inclusion and exclusion criteria. *VRE* vancomycin-resistant *Enterococcus*, *MIC* minimal inhibitory concentration

piperacillin–tazobactam (OR 2.37, 95% CI 1.02–5.53, $p = 0.045$), (Table 3, Supplemental Table 2). The most frequent ADR in patients with concomitant antihistamine usage was daptomycin-related peripheral eosinophilia ($N = 7$), followed by ALT elevation ($N = 4$) and ALP elevation ($N = 4$). The most frequent ADR in patients with concomitant piperacillin–tazobactam was ALP elevation ($N = 15$), followed by ALT elevation ($N = 11$), daptomycin-related peripheral eosinophilia ($N = 7$), and CK elevation ($N = 3$).

DISCUSSION

In this retrospective cohort study, high-dose daptomycin was not associated with an increased rate of ADRs or laboratory abnormalities compared to standard-dose daptomycin.

Our results correlate with previous studies that found no difference in the rates of CK elevation between higher versus lower doses of daptomycin, in which median doses ranged from 6.02 to 10.2 mg/kg [6, 9].

Despite a relatively high rate of ADRs or laboratory abnormalities, daptomycin dose decreases were rare, and there were no permanent cessations. Further, RUCAM causality scoring suggested hepatic dysfunction was not clearly attributable to daptomycin. This suggests daptomycin may be associated with a high rate of laboratory abnormalities that are generally subclinical and/or might be attributed to other causes.

Additionally, we found concomitant usage of antihistamines, but not statins, was associated with the composite safety outcome, primarily driven by daptomycin-related peripheral

Table 1 Baseline characteristics of patients included in safety analysis

	Standard dose (N = 76)	High dose (N = 43)	Total (N = 119)	p value
Clinical characteristics				
Age[a], years, mean (SD)	60.8 (14.6)	60.7 (14.0)	60.7 (14.3)	0.99
Gender[a], n (%)				0.09
Female	36 (48.0%)	13 (31.7%)	49 (42.2%)	
Male	39 (52.0%)	28 (68.3%)	67 (57.8%)	
Weight[a], kg, median (IQR)	76.2 (65.2, 91.5)	76.0 (62.1, 88.9)	76.1 (64.0, 91.4)	0.91
Baseline SCr[b], mg/dL, median (IQR)	1.0 (0.7, 1.8)	1.0 (0.8, 1.7)	1.0 (0.7, 1.7)	0.69
Baseline CK[c], U/L, median (IQR)	37 (18, 76)	34 (21, 75)	37 (18, 76)	0.88
Baseline ALT[d], U/L, median (IQR)	26 (14, 62)	28.5 (19, 66)	27 (17, 65)	0.54
Baseline ALP[e], U/L, median (IQR)	177 (96, 283)	154 (84, 283)	161 (84, 283)	0.81
Baseline peripheral eosinophil/WBC[f], %, median (IQR)	1.8 (0.8, 3.0)	1.1 (0.5, 2.1)	1.5 (0.7, 3.0)	0.053
Charlson Comorbidity Index[a], median (IQR)	7 (4, 10)	7 (4.5, 10.5)	7 (4, 10)	0.79
Daptomycin dosing				
Dose, mg/kg, median (IQR)	6.0 (5.4, 6.1)	8.1 (7.9, 9.6)	6.1 (6.0, 8.0)	–
Dose, mg, median (IQR)	410 (330, 450)	580 (500, 700)	450 (388, 513)	< 0.001
Frequency, n (%)				0.03
Q24h	55 (72.4%)	35 (81.4%)	90 (75.6%)	
Q48h	19 (25.0%)	3 (7.0%)	22 (18.5%)	
With hemodialysis	1 (1.3%)	2 (4.7%)	3 (2.5%)	
Other	1 (1.3%)	3 (7.0%)	4 (3.4%)	
Duration, days, median (IQR)	13.5 (7, 23)	16 (10, 44)	15 (8, 35)	0.019
Concomitant medications during infectious course				
Statin[g], n (%)	20 (30.3%)	11 (27.5%)	31 (29.2%)	0.76
Antihistamine, n (%)	16 (21.1%)	5 (11.6%)	21 (17.6%)	0.20

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *CK* creatine kinase, *IQR* interquartile range, *SCr* serum creatinine, *SD* standard deviation, *WBC* white blood cell

[a]N = 75 for standard-dose group, N = 41 for high-dose group, N = 116 for total
[b]N = 75 for standard-dose group, N = 43 for high-dose group, N = 118 for total
[c]N = 57 for standard-dose group, N = 36 for high-dose group, N = 93 for total
[d]N = 53 for standard-dose group, N = 28 for high-dose group, N = 81 for total
[e]N = 47 for standard-dose group, N = 30 for high-dose group, N = 77 for total
[f]N = 54 for standard-dose group, N = 26 for high-dose group, N = 80 for total
[g]N = 66 for standard-dose group, N = 40 for high-dose group, N = 106 for total

Table 2 Safety outcomes of patients treated with standard- versus high-dose daptomycin

	Standard dose (N = 76)	High dose (N = 43)	Total (N = 119)	p value
Safety analysis: patient level				
Patients with ≥ 1 ADR[a], n (%)	24 (32.0%)	13 (32.5%)	37 (32.2%)	0.96
Time to first ADR[a], days, median (IQR)	3 (1, 12.5)	5 (2, 11)	4 (1, 12)	0.48
Safety analysis: ADR level				
ALP elevation[b], n (%)	13 (25.5%)	8 (24.2%)	21 (25.0%)	0.90
Did not meet CTCAE criteria	43 (56.6%)	24 (55.8%)	67 (56.3%)	0.83
CTCAE grade 1	19 (25.0%)	13 (30.2%)	32 (26.9%)	
CTCAE grade 2	10 (13.2%)	5 (11.6%)	15 (12.6%)	
CTCAE grade 3	4 (5.3%)	1 (2.3%)	5 (4.2%)	
Daptomycin dose at time of ADR, mg/kg, median (IQR)	6 (6, 6.2)	8.1 (7.8, 8.8)	6.3 (6.0, 8.0)	< 0.001
Duration of current daptomycin dose at time of ADR, days, median (IQR)	1 (1, 7)	2.5 (1.5, 7)	2 (1, 7)	0.62
Total daptomycin duration at time of ADR, days, median (IQR)	1 (1, 7)	2.5 (1.5, 9)	2 (1, 7)	0.47
ALT elevation[c], n (%)	9 (15.0%)	5 (14.7%)	14 (14.9%)	0.97
Did not meet CTCAE criteria	60 (78.9%)	34 (79.1%)	94 (79.0%)	0.16
CTCAE grade 1	7 (9.2%)	8 (18.6%)	15 (12.6%)	
CTCAE grade 2	5 (6.6%)	1 (2.3%)	6 (5.0%)	
CTCAE grade 3	4 (5.3%)	0 (0.0%)	4 (3.4%)	
Daptomycin dose at time of ADR, mg/kg, median (IQR)	6.0 (6.0, 6.1)	8.5 (8.1, 10.0)	6.1 (6.0, 8.1)	0.007
Duration of current daptomycin dose at time of ADR, days, median (IQR)	1 (1, 2)	29 (3, 35)	2 (1, 4)	0.005
Total daptomycin duration at time of ADR, days, median (IQR)	1 (1, 2)	31 (11, 38)	2 (1, 11)	0.004
Daptomycin-related peripheral blood eosinophilia[d], n (%)	10 (16.7%)	5 (16.1%)	15 (16.5%)	0.95
Daptomycin dose at time of ADR, mg/kg, median (IQR)	6.1 (5.2, 6.3)	8.1 (8.0, 8.5)	6.3 (6.0, 8.0)	0.003
Duration of current daptomycin dose at time of ADR, days, median (IQR)	12.5 (8, 17)	13 (4, 20)	13 (4, 20)	0.75
Total daptomycin duration at time of ADR, days, median (IQR)	12.5 (8, 17)	13 (5, 23)	13 (5, 23)	0.83

Table 2 continued

	Standard dose (N = 76)	High dose (N = 43)	Total (N = 119)	p value
CK elevation[e], n (%)	3 (4.5%)	0 (0.0%)	3 (2.9%)	0.18
Daptomycin dose at time of ADR, mg/kg, median (IQR)	6 (6, 6)	–	6 (6, 6)	–
Duration of current daptomycin dose at time of ADR, days, median (IQR)	2 (1, 15)	–	2 (1, 15)	–
Total daptomycin duration at time of ADR, days, median (IQR)	2 (1, 15)	–	2 (1, 15)	–
Eosinophilic pneumonitis, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–

ADR adverse drug reaction, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *CK* creatine kinase, *CTCAE* Common Terminology Criteria for Adverse Events, *IQR* interquartile range
[a]N = 75 for standard-dose group, N = 40 for high-dose group, N = 115 for total
[b]N = 51 for standard-dose group, N = 33 for high-dose group, N = 84 for total
[c]N = 60 for standard-dose group, N = 34 for high-dose group, N = 94 for total
[d]N = 60 for standard-dose group, N = 31 for high-dose group, N = 91 for total
[e]N = 66 for standard-dose group, N = 38 for high-dose group, N = 104 for total

eosinophilia; other studies have reported concomitant statin and antihistamine use as risk factors for CK elevation, myopathy, and rhabdomyolysis [9, 14, 15]. We also found that concomitant piperacillin–tazobactam was associated with the composite outcome, primarily driven by LFT elevation. Further research is needed to better elucidate the effects of antihistamines, statins, and piperacillin–tazobactam used concomitantly with daptomycin.

This study is not without limitations. As a retrospective observational study, our findings were subject to confounding factors, including baseline differences in comorbidities, severity of illness, and concomitant medications, as well as the logistical limitations of chart review. Only a relatively small sample size met inclusion criteria, which may have impacted our ability to detect statistically meaningful differences; however, a 0.5% absolute difference in composite outcome occurrence is likely not clinically meaningful. Additionally, it is possible that the definitions used for the composite endpoint could have led to attribution of daptomycin-mediated ADR when elevated laboratory values may have reflected baseline abnormalities or derangements from other causes. Our use of RUCAM scoring aimed to mitigate this. Finally, given a median dose of 8.1 mg/kg (IQR 7.9, 9.6) in our high-dose cohort, we cannot draw strong conclusions regarding doses in the 10–12 mg/kg range recommended for SDD isolates. Of note, one prior study reported a 3.9% rate of highly elevated CK (> 2000 U/L) with daptomycin doses ≥ 11 mg/kg compared to a 1.1% rate with doses 8 to < 11 mg/kg [8].

CONCLUSION

These limited data suggest that the occurrence of ADRs or laboratory abnormalities with daptomycin did not appear dose-related and rarely resulted in therapy modification. Coupled with previous literature demonstrating daptomycin's dose-dependent efficacy, our safety findings support the use of 8–10 mg/kg of daptomycin for SDD enterococcal infections.

Table 3 Univariate and multivariable logistic regression assessing associations with the composite outcome

Characteristics	Univariate		Multivariable	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Clinical characteristics				
Age	0.99 (0.96–1.02)	0.53		
Gender				
Female	Reference			
Male	1.40 (0.63–3.13)	0.41		
Weight	1.00 (0.98–1.01)	0.83		
Baseline SCr	0.73 (0.48–1.11)	0.14		
Charlson Comorbidity Index	0.97 (0.88–1.07)	0.60		
Daptomycin dosing				
Average dose	1.13 (0.89–1.43)	0.31		
Standard vs. high dose				
Standard dose	Reference		Reference	
High dose	1.02 (0.45–2.32)	0.96	1.11 (0.46–2.69)	0.81
Frequency				
Q24h	Reference			
Q48h	0.45 (0.14–1.45)	0.18		
With hemodialysis	0.95 (0.08–10.91)	0.97		
Other	1.90 (0.26–14.17)	0.53		
Concomitant medications during infectious course				
Statin	0.70 (0.27–1.78)	0.45		
Antihistamine	2.88 (1.09–7.57)	0.033	3.24 (1.16–9.02)	0.025
Antibiotics				
Ampicillin	4.40 (0.39–50.15)	0.23		
Piperacillin–tazobactam	2.48 (1.11–5.52)	0.026	2.37 (1.02–5.53)	0.045
Cefazolin	1.06 (0.09–12.03)	0.96		
Ceftriaxone	0.66 (0.22–1.97)	0.45		
Cefepime	0.96 (0.42–2.21)	0.92		
Ceftazidime–avibactam	4.40 (0.39–50.15)	0.23		
Ceftolozane–tazobactam	11.05 (0.26–464.89)	0.21		
Ertapenem	1.15 (0.48–2.73)	0.75		
Meropenem	1.25 (0.49–3.16)	0.64		
Ciprofloxacin	3.91 (0.88–17.33)	0.073		

Table 3 continued

Characteristics	Univariate		Multivariable	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Levofloxacin	3.35 (0.54–20.99)	0.20		
Vancomycin	1.15 (0.51–2.61)	0.73		
Linezolid	0.35 (0.07–1.66)	0.19		
Gentamicin	11.05 (0.26–464.89)	0.21		
Metronidazole	0.90 (0.38–2.10)	0.80		
Other antibiotic	4.32 (1.18–15.83)	0.027	4.04 (1.04–15.62)	0.043

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Declarations

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