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High-Dose Daptomycin Therapy for Left-Sided Infective Endocarditis: a Prospective Study from the International Collaboration on Endocarditis

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The use of daptomycin in Gram-positive left-sided infective endocarditis (IE) has significantly increased. The purpose of this study was to assess the influence of high-dose daptomycin on the outcome of left-sided IE due to Gram-positive pathogens. This was a prospective cohort study based on 1,112 cases from the International Collaboration on Endocarditis (ICE)-Plus database and the ICE-Daptomycin Substudy database from 2008 to 2010. Among patients with left-sided IE due to *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterococcus faecalis*, we compared those treated with daptomycin (cohort A) to those treated with standard-of-care (SOC) antibiotics (cohort B). The primary outcome was in-hospital mortality. Time to clearance of bacteremia, 6-month mortality, and adverse events (AEs) ascribable to daptomycin were also assessed. There were 29 and 149 patients included in cohort A and cohort B, respectively. Baseline comorbidities did not differ between the two cohorts, except for a significantly higher prevalence of diabetes and previous episodes of IE among patients treated with daptomycin. The median daptomycin dose was 9.2 mg/kg of body weight/day. Two-thirds of the patients treated with daptomycin had failed a previous antibiotic regimen. In-hospital and 6-month mortalities were similar in the two cohorts. In cohort A, median time to clearance of methicillin-resistant *S. aureus* (MRSA) bacteremia was 1.0 day, irrespective of daptomycin dose, representing a significantly faster bacteremia clearance compared to SOC (1.0 versus 5.0 days; $P < 0.01$). Regimens with higher daptomycin doses were not associated with increased incidence of AEs. In conclusion, higher-dose daptomycin may be an effective and safe alternative to SOC in the treatment of left-sided IE due to common Gram-positive pathogens.

Infective endocarditis (IE) of left-sided cardiac valves is characterized by high morbidity and mortality. Recent studies indicate that the incidence of this serious infection is relatively high among life-threatening syndromes, ranging from 5.0 to 7.9 cases per 100.000 person-years (1–4). Additionally, the rate of antimicrobial resistance among common Gram-positive IE pathogens has increased (5, 6), creating an urgent need for antibiotics with activity against such resistant pathogens. In 2006, the U.S. Food and Drug Administration (FDA) approved daptomycin for the treatment of bacteremia and right-sided IE caused by *Staphylococcus aureus* (7, 8). Since that time, the successful use of daptomycin in the treatment of IE due to other Gram-positive organisms, including coagulase-negative staphylococci (CoNS), streptococci, *Enterococcus faecalis*, and *Corynebacterium*, has been reported (9–13). Recent literature suggests that daptomycin may be useful in the treatment of left-sided IE as well as right-sided IE (14–16). Despite these individual reports, there has not been a prospective comparative evaluation of daptomycin in the treatment of Gram-positive IE in well-defined clinical left-sided IE cases. In this observational prospective cohort study, we assessed the influence of daptomycin on the outcome of Gram-positive left-sided IE in comparison to standard-of-care (SOC) approaches.

MATERIALS AND METHODS

Study design. This observational multicenter prospective cohort study is based on data within the International Collaboration on Endocarditis Plus (ICE-Plus) and the ICE Daptomycin Substudy (ICE-DS). The ICE-Plus database contains prospective data on 1,112 patients with IE from 29 sites in 16 countries collected between 1 September 2008 and 31 December 2010. The ICE-DS contains more specific antibiotic-related prospective data on 64 patients with IE treated with daptomycin during the same period. Both the ICE-Plus and the ICE-DS databases are maintained at the Duke Clinical Research Institute (DCRI), which serves as the coordinating center for the ICE studies, with institutional review board approvals from the Duke University School of Medicine and the participating ICE-Plus sites. A detailed description of the ICE organization and methodologies for data collection and cataloguing has been provided before (17).

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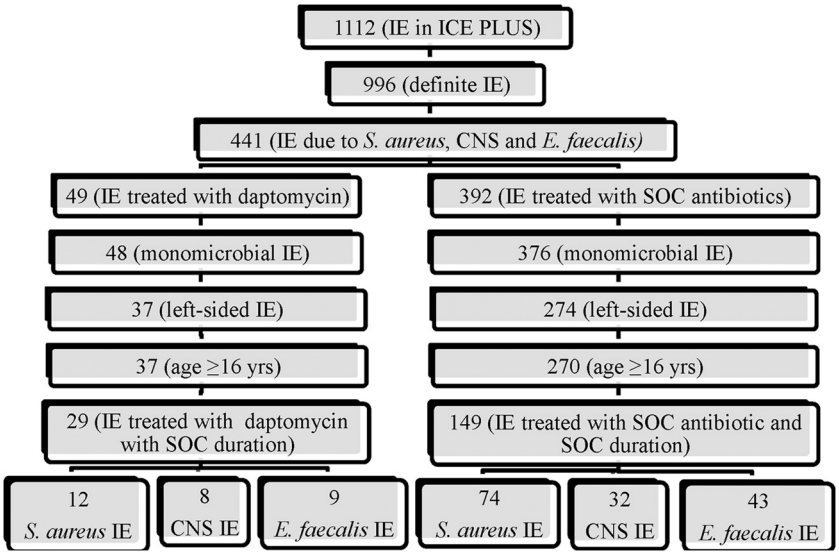

FIG 1 Study population.

Study population. Eligible patients were 16 years of age or older and met all of the following criteria: (i) diagnosis of "definite IE" by the modified Duke criteria (18); (ii) monomicrobial IE caused by *S. aureus*, coagulase-negative staphylococci, or *E. faecalis*; (iii) left-sided IE (defined clinically and/or echocardiographically); and (iv) duration of antibiotic therapy of >50% of the course recommended by the American Heart Association (AHA) guidelines for the treatment of IE (19). To reduce survivor bias, patients whose antibiotic therapy was discontinued because of death were included, even if the duration of treatment was ≤50% of the course recommended above (19). Patients treated with daptomycin were defined as cohort A, while patients treated with SOC antibiotics for Gram-positive IE, according to the AHA guidelines, were defined as cohort B (19). Specifically, the following antibiotic choices were considered SOC: antistaphylococcal penicillins for methicillin-susceptible *S. aureus* (MSSA), vancomycin for methicillin-resistant *S. aureus* (MRSA), ampicillin plus an aminoglycoside for ampicillin-susceptible *E. faecalis*, and vancomycin plus an aminoglycoside for ampicillin-resistant *E. faecalis*. Since CoNS can exhibit heterogeneity with respect to methicillin resistance, vancomycin was considered the SOC antibiotic for IE caused by CoNS, irrespective of the reported methicillin susceptibility profile from the individual clinical microbiology laboratories. Patients with IE due to vancomycin-resistant enterococci were excluded from this study.

A case report form containing 275 variables, with additional variables for the ICE-Daptomycin Substudy, was developed by the ICE group according to standard definitions (17, 20, 21). Data were collected prospectively for each patient by site investigators during the index hospitalization and were then sent to the coordinating center for data entry.

Definitions. Time to clearance of bacteremia was defined as number of days between the first positive blood culture and the first negative blood culture for the causative agents of IE. Significant creatine phosphokinase (CPK) elevation was defined in our study as an elevation greater than 400 IU/liter (normal range < 50 IU/ml). This CPK metric is based on data from a prior study of daptomycin usage in *S. aureus* bacteremia (8). CPK levels greater than 400 IU/liter in the 72 h immediately after surgery were not reported. Peripheral nervous system disorders were defined as paresthesias, dysesthesias, and peripheral neuropathies. Cases of eosinophilic pneumonia in patients receiving daptomycin were characterized by fever, dyspnea, new infiltrates on chest imaging, bronchoalveolar lavage fluid with >25% eosinophils, and clinical improvement following daptomycin withdrawal. Patients were judged by each site principal investigator to have "clinical failure" if they had no response to the antimicrobial treatment on the basis of ongoing fever, leukocytosis, or other clinical parameters. The definition of clinical failure required the exclusion of any other possible cause of ongoing fever and leukocytosis other than failure to resolve the manifestations of infective endocarditis (such as catheter-related bloodstream infection, *Clostridium difficile*-associated diarrhea, urinary tract infection, or drug fever). "Persistent bacteremia" was defined using Duke Endocarditis Service Criteria as persistence of positive blood cultures after 72 h of organism-specific targeted antibacterial treatment (22). The 6-month mortality was defined as the mortality rate in the period from hospital admission to 180 days after hospital discharge. Length of hospital stay (LOS) was defined as number of days from the date in which antibiotic treatment for IE was started to the date of discharge.

Study objectives. This study principally aimed to compare in-hospital mortality rates between patients treated with daptomycin and patients treated with SOC for left-sided IE due to *S. aureus*, CoNS, and *E. faecalis*. Secondary objectives of the study included the following: (i) to compare 6-month mortality rates of patients in cohort A and patients in cohort B, (ii) to determine if there was a relationship between dose of daptomycin and time to clearance of bacteremia and/or adverse events in cohort A, and (iii) to assess the incidence of specific adverse events which have been related to the use of daptomycin, including significant elevation of CPK, peripheral neuropathy, and eosinophilic pneumonia (8, 9, 13, 16).

Statistical analysis. Continuous variables are presented as medians with interquartile ranges (IQR). Categorical variables are presented as frequencies and percentages of the specified group. Comparisons between groups were made with the Fisher exact test or Kruskal-Wallis test as appropriate. A two-sided P value of <0.05 was considered statistically significant. Since in-hospital and 6-month mortality were common outcomes in our study, and the use of an adjusted odds ratio may overstate the relative risk, a log-binomial model was used to compute the adjusted relative risk of these outcomes. Variables found to have the strongest univariable association with in-hospital mortality and 6-month mortality ($P < 0.05$) were entered into the final model in order to have at least 10 events per variable. The variable "Cohort A" was entered in the models to assess the risk of in-hospital and 6-month mortality even though the P value was >0.05 in univariate analysis. Relative risks (RR) with 95% confidence intervals (95% CI) were calculated. Statistical analyses were performed using SAS Enterprise Guide (version 5.1; SAS Institute, Cary, NC).

RESULTS

Of the 1,112 patients available in the ICE-Plus and ICE DS databases, there were 996 patients with definite IE. IE was due to *S. aureus*, CoNS, or *E. faecalis* in 441 of these patients; 49 were treated with daptomycin, and 392 were treated with a different antibiotic regimen. Of the patients treated with daptomycin, the following were excluded: polymicrobial infection ($n = 1$), non-left-sided IE ($n = 11$), and duration of treatment of <50% of the duration recommended by the AHA ($n = 8$). Of the 392 patients not receiving daptomycin, the following were excluded: polymicrobial IE ($n = 16$), non-left-sided IE ($n = 102$), age of <16 years ($n = 4$), and antibiotic regimens which did not meet study criteria, as described above ($n = 121$). Thus, there were 29 evaluable subjects in cohort A and 149 patients in cohort B of this study (Fig. 1). Cohort A and cohort B represented patients from various geographic regions as follows: 17.2% from South America and 82.8% from Europe for cohort A and 7.4% from North America, 10.7% from South America, 4.7% from Australia or New Zealand, 62.4% from Europe, 12.1% from Asia, and 2.7% from Africa for cohort B.

***S. aureus* IE.** Daptomycin was used as the main therapy for 14% of patients with *S. aureus* IE who fulfilled study criteria (cohort A) (Tables 1 and 2). Methicillin resistance was present in 58% of strains in cohort A and 24% of strains in cohort B ($P = 0.03$).

Among patients with MRSA IE, daptomycin was used as the main therapy in approximately one-quarter (28.0%). None of the patients who were switched from vancomycin to daptomycin had a MRSA strain with decreased susceptibility to vancomycin (i.e., VISA). Prosthetic-valve IE was present in 2 (18.2%) and 14 (18.9%) of the subjects in cohorts A and B, respectively. Baseline characteristics among patients with *S. aureus* IE were similar in the daptomycin and SOC groups except that patients with *S. aureus* IE who had diabetes mellitus and connective-tissue diseases were more likely to be treated with daptomycin than SOC therapy (63.6% versus 31.5% [$P = 0.04$] and 25.0% versus 4.1% [$P = 0.03$], respectively). IE-related complications, rate of surgical treatment, in-hospital mortality, and 6-month mortality were similar for patients with *S. aureus* IE treated with daptomycin (cohort A) versus SOC antibiotics (cohort B). However, among patients with MRSA IE, a significantly shorter time to clearance of bacteremia and shorter LOS were observed in patients treated with daptomycin versus SOC antibiotics (1.0 day [range, 1.0 to 2.0 days] versus 5.0 days [range, 3.0 to 9.0 days] [$P < 0.01$] and 33.0 days [range, 19.0 to 49.0 days] versus 64.5 days [range, 45.0 to 126.0 days] [$P = 0.04$]).

CoNS IE. Of the 40 patients with CoNS IE included in this study, 8 (20.0%) were treated with daptomycin. A substantial proportion of patients in cohorts A and B had prosthetic-valve IE (4 [50.0%] and 16 [53.3%], respectively). Baseline characteristics, IE-related complications, rate of surgical treatment, time to clearance of bacteremia, in-hospital mortality, 6-month mortality, and LOS were similar among patients with CoNS IE treated with daptomycin (cohort A) versus SOC (cohort B) (Table 3). Although not statistically significant, patients with CoNS IE treated with daptomycin had a lower rate of stroke syndromes than patients treated with SOC (0 [0.0%] versus 8 [26.7%]; $P = 0.16$). Similar findings were obtained when only patients with methicillin-resistant CoNS IE were analyzed.

TABLE 1 Clinical characteristics of infective endocarditis due to *Staphylococcus aureus* in cohort A (patients treated with daptomycin) and in cohort B (patients treated with SOC antibiotics)[a]

Parameter	Cohort A ($n = 12$)	Cohort B ($n = 74$)	*P* value
Baseline characteristics			
Age, yrs (median, IQR)	62.5 (54.0–72.5)	60.5 (44.0–73.0)	0.60
Male, *n* (%)	5/11 (45.5)	52/73 (71.2)	0.16
Moderate/severe renal disease, *n* (%)	4/12 (33.3)	11/72 (15.3)	0.21
Dialysis, *n* (%)	2/8 (25.0)	5/21 (23.8)	1.00
Diabetes mellitus, *n* (%)	7/11 (63.6)	23/73 (31.5)	**0.04**
Chronic pulmonary diseases, *n* (%)	1/12 (8.3)	14/73 (19.2)	0.68
History of coronary artery disease, *n* (%)	3/11 (27.3)	11/73 (15.1)	0.38
Moderate/severe liver disease, *n* (%)	1/12 (8.3)	4/72 (5.6)	0.55
Connective tissue disease, *n* (%)	3/12 (25.0)	3/74 (4.1)	**0.03**
Chronic immunosuppressive therapy, *n* (%)	2/12 (16.7)	4/74 (5.4)	0.20
Cancer, *n* (%)	1/12 (8.3)	7/74 (9.5)	1.00
History of i.v. drug use, *n* (%)	0/12 (0.0)	6/74 (8.1)	0.59
Predisposing conditions			
Previous IE, *n* (%)	2/12 (16.7)	5/71 (7.0)	0.27
Congenital heart disease, *n* (%)	1/12 (8.3)	6/71 (8.5)	1.00
History of rheumatic valve, *n* (%)	0/11 (0.0)	3/71 (4.2)	1.00
Native valve predisposition, *n* (%)	2/9 (22.2)	21/68 (30.9)	0.72
IE type			
Native-valve IE, *n* (%)	9/11 (81.8)	60/74 (81.1)	1.00
Prosthetic-valve IE, *n* (%)	2/11 (18.2)	14/74 (18.9)	1.00
Intracardiac complications			
Perforation, *n* (%)	0/12 (0.0)	14/74 (18.9)	0.20
Abscess, *n* (%)	3/12 (25.0)	21/74 (28.4)	1.00
Intracardiac fistula, *n* (%)	0/12 (0.0)	2/74 (2.7)	1.00
Complication and management data			
Stroke, *n* (%)	5/11 (45.5)	21/72 (29.2)	0.31
Embolization, nonstroke, *n* (%)	5/12 (41.7)	34/70 (48.6)	0.66
Recurrent embolization, *n* (%)	2/12 (16.7)	6/65 (9.2)	0.60
Persistent bacteremia, *n* (%)	2/11 (18.2)	17/67 (25.4)	1.00
New or worsening heart failure, *n* (%)	2/12 (16.7)	22/70 (31.4)	0.49
New conduction abnormalities, *n* (%)	0/12 (0.0)	9/71 (12.7)	0.34
Surgical indication, *n* (%)	10/12 (83.3)	57/74 (77.0)	1.00
Surgical therapy, *n* (%)	4/12 (33.3)	32/72 (44.4)	0.47
Time to clearance of bacteremia, days, median (IQR)	1.5 (1.0–2.0)	3.0 (1.0–7.0)	0.10
Length of hospital stay in survivors, days, median (IQR)	46.0 (19.0–53.0)	46.0 (34.0–62.0)	0.35
In-hospital mortality, *n* (%)	3/12 (25.0)	28/74 (37.8)	0.52
6-mo mortality, *n* (%)	5//7 (71.4)	31/55 (56.4)	0.69

[a] Only percentages less than 1% are carried to the first decimal place. i.v., intravenous. Statistically significant associations are presented in boldface.

***E. faecalis* IE.** Daptomycin was used in 17.3% of patients with vancomycin-susceptible *E. faecalis* IE in our study population. Ampicillin resistance was detected in 1 (11.1%) and 2 (4.6%) strains in cohorts A and B, respectively. A higher proportion of prosthetic-valve IE was seen among patients treated with daptomycin than with SOC antibiotics (7 [77.8%] versus 15 [34.9%]; $P = 0.03$). Overall, there was a high prevalence of comorbid conditions (i.e., diabetes mellitus, chronic pulmonary disease, coronary artery disease, and cancer) among patients with *E. faecalis* IE in both cohorts A and B. History of a previous episode of IE was significantly more common in cohort A than in cohort B. The proportion of patients receiving valve surgery was not statistically

TABLE 2 Clinical characteristics of infective endocarditis due to MSSA and MRSA in cohort A (patients treated with daptomycin) and in cohort B (patients treated with vancomycin for MRSA infection and nafcillin-oxacillin for MSSA infection)[a]

Parameter	MSSA			MRSA		
	Cohort A ($n = 5$)	Cohort B ($n = 56$)	*P* value	Cohort A ($n = 7$)	Cohort B ($n = 18$)	*P* value
Baseline characteristics						
Age, yrs (median, IQR)	55.0 (53.0–63.0)	61.5 (44.0–73.5)	0.92	71.0 (56.0–73.0)	58.0 (46.0–71.0)	0.36
Male, *n* (%)	1/4 (25.0)	40/56 (71.4)	0.09	4/7 (57.1)	12/17 (70.6)	0.65
Moderate/severe renal disease, *n* (%)	2/5 (40.0)	5/55 (9.1)	0.09	2/7 (28.6)	6/17 (35.3)	1.00
Dialysis, *n* (%)	1/4 (25.0)	2/11 (18.2)	1.00	1/4 (25.0)	3/10 (30.0)	1.00
Diabetes mellitus, *n* (%)	2/5 (40.0)	16/55 (29.1)	0.63	5/6 (83.3)	7/18 (38.9)	0.15
Chronic pulmonary diseases, *n* (%)	1/5 (20.0)	6/55 (10.9)	0.47	0/7 (0.0)	8/18 (44.4)	0.06
History of coronary artery disease, *n* (%)	2/5 (40.0)	8/56 (14.3)	0.18	1/6 (16.7)	3/17 (17.6)	1.00
Moderate/severe liver disease, *n* (%)	0/5 (0.0)	4/55 (7.3)	1.00	1/7 (14.3)	0/17 (0.0)	0.29
Connective tissue disease, *n* (%)	2/5 (40.0)	2/56 (3.6)	0.03	1/7 (14.3)	1/18 (5.6)	0.49
Chronic immunosuppressive therapy, *n* (%)	2/5 (40.0)	2/56 (3.6)	0.03	0/7 (0.0)	2/18 (11.1)	1.00
Cancer, *n* (%)	1/5 (20.0)	3/56 (5.4)	0.30	0/7 (0.0)	4/18 (22.2)	0.29
History of i.v. drug use, *n* (%)	0/5 (0.0)	4/56 (7.1)	1.00	0/7 (0.0)	2/18 (11.1)	1.00
Predisposing conditions						
Previous IE, *n* (%)	2/5 (40.0)	3/53 (5.7)	0.05	0/7 (0.0)	2/18 (11.1)	1.00
Congenital heart disease, *n* (%)	1/5 (20.0)	6/53 (11.3)	0.49	0/7 (0.0)	0/18 (0.0)	
History of rheumatic valve, *n* (%)	0/5 (0.0)	2/54 (3.7)	1.00	0/6 (0.0)	1/17 (5.9)	1.00
Native valve predisposition, *n* (%)	1/4 (25.0)	14/52 (26.9)	1.00	1/5 (20.0)	7/16 (43.8)	0.61
IE type						
Native-valve IE, *n* (%)	3/4 (75.0)	46/56 (82.1)	0.57	6/7 (85.7)	14/18 (77.8)	1.00
Prosthetic-valve IE, *n* (%)	1/4 (25.0)	10/56 (17.9)	0.57	1/7 (14.3)	4/18 (22.2)	1.00
Intracardiac complications						
Perforation, *n* (%)	0/5 (0.0)	10/56 (17.8)	0.58	0/7 (0.0)	4/18 (22.2)	0.29
Abscess, *n* (%)	1/5 (20.0)	17/56 (30.4)	1.00	2/7 (28.6)	4/18 (22.2)	1.00
Intracardiac fistula, *n* (%)	0/5 (0.0)	10/56 (17.9)	0.58	0/7 (0.0)	2/18 (11.1)	1.00
Complication and management data						
Stroke, *n* (%)	3/5 (60.0)	17/54 (31.5)	0.32	2/6 (33.3)	4/18 (22.2)	0.62
Embolization, nonstroke, *n* (%)	2/5 (40.0)	26/53 (49.1)	1.00	3/7 (42.8)	8/17 (47.1)	1.00
Recurrent embolization, *n* (%)	2/5 (40.0)	3/47 (6.4)	0.07	0/7 (0.0)	3/18 (16.7)	0.53
Persistent bacteremia, *n* (%)	2/5 (40.0)	8/50 (16.0)	0.22	0/6 (0.0)	9/17 (52.9)	0.04
New or worsening heart failure, *n* (%)	0/5 (0.0)	18/53 (34.0)	0.31	2/7 (28.6)	4/17 (23.5)	1.00
New conduction abnormalities, *n* (%)	0/5 (0.0)	6/54 (11.1)	1.00	0/7 (0.0)	3/17 (17.7)	0.53
Surgical indication, *n* (%)	4/5 (80.0)	41/56 (73.2)	1.00	6/7 (85.7)	16/18 (88.9)	1.00
Surgical therapy, *n* (%)	2/5 (40.0)	22/54 (40.7)	1.00	2/7 (28.6)	10/18 (55.6)	0.38
Time to clearance of bacteremia, days, median (IQR)	6.0 (1.0–7.0)	2.0 (1.0–4.5)	0.53	1.0 (1.0–2.0)	5.0 (3.0–9.0)	<0.01
Length of hospital stay in survivors, days, median (IQR)	77.0 (17.0–99.0)	43.0 (33.0–52.0)	0.45	33.0 (19.0–49.0)	64.5 (45.0–126.0)	0.04
In-hospital mortality, *n* (%)	2/5 (40.0)	20/56 (35.7)	1.00	1/7 (14.3)	8/18 (44.4)	0.35
6-mo mortality, *n* (%)	3/3 (100.0)	23/43 (53.5)	0.25	2/4 (50.0)	8/12 (66.7)	0.60

[a] Only percentages less than 1% are carried to the first decimal place.

significantly different in the two cohorts (4 [44.4%] versus 26 [60.5%]; $P = 0.47$) (Table 4). Patients with *E. faecalis* IE treated with daptomycin had shorter LOS than those treated with SOC antibiotics (17.5 days [range, 13.5 to 19.5 days] versus 31.0 days [range, 19.0 to 50.0 days]; $P = 0.02$). The rate of bacteremia clearance did not differ between the two cohorts (2.0 days [range, 1.5 to 3.0 days] versus 3.0 days [range, 1.5 to 5.0 days]; $P = 0.33$). There was no significant difference in the in-hospital mortality and 6-month mortality between cohorts A and B.

In-hospital mortality and 6-month mortality. While several variables were associated with in-hospital mortality on univariable analysis (Table 5), log-binomial analysis demonstrated that in-hospital mortality was independently associated with an age of ≥60 years, moderate to severe renal disease, and presence of surgical indication for valve replacement. In-hospital mortality did not have an association with daptomycin treatment (RR, 0.8; 95% CI, 0.4 to 1.3; *P* value, 0.35). Follow-up data were available for 135/178 patients (75.8% of the study population). The 6-month mortality rate was significantly associated with an age of >60 years, moderate to severe renal disease, diabetes, and moderate to severe liver disease. Nonstroke embolization was significantly more common among patients alive at 6 months. Of these variables, only moderate to severe liver disease was independently associated with 6-month mortality (RR, 1.7; 95% CI, 1.3 to 1.9; *P* value, 0.03). Daptomycin treatment did not differentially impact 6-month mortality in comparison to SOC therapy. Similarly, surgical therapy was not associated with in-hospital or 6-month mortality (Tables 5 and 6).

TABLE 3 Clinical characteristics of infective endocarditis due to CoNS and methicillin-resistant CoNS in cohort A (patients treated with daptomycin) and cohort B (patients treated with vancomycin)[a]

Parameter	CoNS			MR CoNS		
	Cohort A ($n = 8$)	Cohort B ($n = 32$)	*P* value	Cohort A ($n = 5$)	Cohort B ($n = 17$)	*P* value
Baseline characteristics						
Age, yrs (median, IQR)	62.5 (48.5–75.0)	64.5 (51.0–75.5)	0.84	58.0 (45.0–75.0)	72.0 (62.0–77.0)	0.06
Male, *n* (%)	7/8 (87.5)	16/32 (50.0)	0.11	1/5 (20.0)	7/17 (41.2)	0.61
Moderate/severe renal disease, *n* (%)	2/8 (25.0)	5/30 (16.7)	0.62	0/5 (0.0)	3/15 (20.0)	0.54
Dialysis, *n* (%)	1/4 (25.0)	2/17 (11.8)	0.49	0/1 (0.0)	1/8 (12.5)	1.00
Diabetes mellitus, *n* (%)	5/8 (62.5)	12/32 (37.5)	0.25	2/5 (40.0)	9/17 (52.9)	1.00
Chronic pulmonary diseases, *n* (%)	4/8 (50.0)	5/32 (15.6)	0.06	2/5 (40.0)	3/17 (17.7)	0.55
History of coronary artery disease, *n* (%)	2/8 (25.0)	11/32 (34.4)	1.00	1/5 (20.0)	7/17 (41.2)	0.61
Moderate/severe liver disease, *n* (%)	0/8 (0.0)	0/31 (0.0)		0/5 (0.0)	0/16 (0.0)	
Connective tissue disease, *n* (%)	0/8 (0.0)	1/31 (3.2)	1.00	0/5 (0.0)	1/16 (6.3)	1.00
Chronic immunosuppressive therapy, *n* (%)	0/8 (0.0)	1/31 (3.2)	1.00	0/5 (0.0)	0/16 (0.0)	
Cancer, *n* (%)	2/8 (25.0)	3/31 (9.7)	0.27	1/5 (20.0)	2/17 (11.8)	1.00
History of i.v. drug use, *n* (%)	0/8 (0.0)	2/30 (6.7)	1.00	0/5 (0.0)	0/16 (0.0)	
Predisposing conditions						
Previous IE, *n* (%)	0/8 (0.0)	2/31 (6.5)	1.00	0/5 (0.0)	0/16 (0.0)	
Congenital heart disease, *n* (%)	1/8 (12.5)	3/31 (9.7)	1.00	0/5 (0.0)	0/17 (0.0)	
History of rheumatic valve, *n* (%)	2/8 (25.0)	4/28 (14.3)	0.60	2/5 (40.0)	3/16 (18.8)	0.55
Native valve predisposition, *n* (%)	4/8 (50.0)	15/29 (51.7)	1.00	2/5 (40.0)	7/16 (43.8)	1.00
IE type						
Native-valve IE, *n* (%)	4/8 (50.0)	14/30 (46.7)	1.00	3/5 (60.0)	5/16 (31.3)	0.33
Prosthetic-valve IE, *n* (%)	4/8 (50.0)	16/30 (53.3)	1.00	2/5 (40.0)	11/16 (68.8)	0.33
Intracardiac complications						
Perforation, *n* (%)	2/8 (25.0)	7/32 (21.9)	1.00	0/5 (0.0)	2/17 (11.8)	1.00
Abscess, *n* (%)	3/8 (37.5)	7/31 (22.6)	0.40	2/5 (40.0)	4/17 (23.5)	0.59
Intracardiac fistula, *n* (%)	0/8 (0.0)	0/31 (0.0)		0/5 (0.0)	0/17 (0.0)	
Complication and management data						
Stroke, *n* (%)	0/8 (0.0)	8/30 (26.7)	0.16	0/5 (0.0)	5/15 (33.3)	0.27
Embolization, nonstroke, *n* (%)	0/7 (0.0)	7/32 (21.9)	0.31	0/4 (0.0)	4/17 (23.5)	0.55
Recurrent embolizations, *n* (%)	0/8 (0.0)	1/31 (3.2)	1.00	0/5 (0.0)	0/16 (0.0)	
New or worsening heart failure, *n* (%)	5/8 (62.5)	13/32 (40.6)	0.43	3/5 (60.0)	5/17 (29.4)	0.31
New conduction abnormalities, *n* (%)	1/8 (12.5)	3/32 (9.4)	1.00	0/5 (0.0)	3/17 (17.7)	1.00
Surgical indications, *n* (%)	8/8 (100.0)	27/32 (84.4)	0.56	5/5 (100.0)	13/17 (76.5)	0.54
Surgical therapy, *n* (%)	4/8 (50.0)	20/32 (62.5)	0.69	3/5 (60.0)	9/17 (52.9)	1.00
Persistent bacteremia, *n* (%)	2/6 (33.3)	8/29 (27.6)	1.00	2/3 (66.7)	4/16 (25.0)	0.22
Time to clearance of bacteremia, days, median (IQR)	3.0 (1.0–5.0)	2.0 (1.5–4.0)	0.97	5.0 (5.0–5.0)	3.0 (2.0–5.0)	0.34
Length of hospital stay in survivors, days, median (IQR)	26.0 (22.5–50.0)	34.0 (27.0–50.0)	0.50	26.0 (22.5–50.0)	42.0 (21.0–61.0)	0.57
In-hospital mortality, *n* (%)	4/8 (50.0)	10/31 (32.3)	0.42	1/5 (20.0)	9/16 (56.3)	0.31
6-mo mortality, *n* (%)	4/5 (80.0)	11/26 (42.3)	0.17	1/2 (50.0)	10/14 (71.4)	1.00

[a] Only percentages less than 1% are carried to the first decimal place. MR CoNS, methicillin-resistant coagulase-negative staphylococci; i.v., intravenous.

Daptomycin dose regimens. Patients who were treated with daptomycin received a median daily dose of 9.2 mg/kg (range, 7.7 to 10.0 mg/kg) for 39 days (range, 25.0 to 43.0 days). Daptomycin was used as a second-line treatment in 19 (67.9%) patients for the following reasons: clinical failure of the initial regimen ($n = 3$), persistently positive blood cultures ($n = 3$), adverse events ($n = 4$), and unspecified reasons ($n = 9$). While discontinuation of daptomycin therapy was reported for 4 (14.3%) patients, in none of these patients was the interruption due to clinical or microbiological failure.

Daptomycin-specific adverse events occurred in 3 (10.7%) patients (Table 7). When the cohort was divided into treatment with <8 mg/kg/day versus ≥8 mg/kg/day of daptomycin, the dosage of daptomycin was not significantly associated with in-hospital mortality, 6-month mortality, clinical or microbiological failure, time to clearance of bacteremia, or adverse events. When only patients alive at discharge were analyzed, the durations of therapy were found to be similar among those receiving daptomycin at a dosage of <8 mg/kg/day, compared with ≥8 mg/kg/day (42.0 [range, 42.0 to 43.0] versus 31.0 [range, 23.0 to 43.0] days; $P = 0.21$) (Table 8). Daptomycin was used in combination with a different antimicrobial in 9 patients (31.0%). The

TABLE 4 Clinical characteristics of infective endocarditis due to *Enterococcus faecalis* in cohort A (patients treated with daptomycin) and B (patients treated with ampicillin or vancomycin plus an aminoglycoside)[a]

Parameter	Cohort A ($n = 9$)	Cohort B ($n = 43$)	*P* value
Baseline characteristics			
Age, yrs, median (IQR)	65.0 (56.0–77.0)	64.5 (52.0–74.0)	0.65
Male, *n* (%)	5/9 (55.6)	31/43 (72.1)	0.43
Moderate/severe renal disease, *n* (%)	0/9 (0.0)	9/43 (20.9)	0.33
Dialysis, *n* (%)	0/5 (0.0)	5/23 (21.7)	0.55
Diabetes mellitus, *n* (%)	4/9 (44.4)	6/41 (14.6)	0.07
Chronic pulmonary diseases, *n* (%)	3/9 (33.3)	9/43 (20.9)	0.41
History of coronary artery disease, *n* (%)	2/9 (22.2)	11/41 (26.8)	1.00
Moderate/severe liver disease, *n* (%)	0/9 (0.0)	2/43 (4.7)	1.00
Connective tissue disease, *n* (%)	0/9 (0.0)	1/43 (2.3)	1.00
Chronic immunosuppressive therapy, *n* (%)	0/9 (0.0)	2/43 (4.7)	1.00
Cancer, *n* (%)	2/8 (25.0)	9/43 (20.9)	1.00
History of i.v. drug use, *n* (%)	0/9 (0.0)	2/42 (4.8)	1.00
Predisposing conditions			
Previous IE, *n* (%)	4/9 (44.4)	3/43 (7.0)	**0.01**
Congenital heart disease, *n* (%)	0/9 (0.0)	2/43 (4.7)	1.00
History of rheumatic valve, *n* (%)	2/9 (22.2)	4/42 (9.5)	0.28
Native valve predisposition, *n* (%)	3/8 (37.5)	17/40 (42.5)	1.00
IE type			
Native-valve IE, *n* (%)	2/9 (22.2)	28/43 (65.1)	**0.03**
Prosthetic-valve IE, *n* (%)	7/9 (77.8)	15/43 (34.9)	**0.03**
Intracardiac complications			
Perforation, *n* (%)	0/9 (0.0)	8/43 (18.6)	0.32
Abscess, *n* (%)	2/9 (22.2)	10/42 (23.8)	1.00
Intracardiac fistula, *n* (%)	1/9 (11.1)	0/41 (0.0)	0.18
Complication and management data			
Stroke, *n* (%)	2/9 (22.2)	6/43 (14.0)	0.61
Embolization, nonstroke, *n* (%)	1/9 (11.1)	8/42 (18.6)	1.00
Recurrent embolizations, *n* (%)	0/9 (0.0)	1/43 (2.4)	1.00
New or worsening heart failure, *n* (%)	4/9 (44.4)	17/43 (39.5)	1.00
New conduction abnormalities, *n* (%)	3/9 (33.3)	4/43 (9.3)	0.09
Surgical indication, *n* (%)	7/9 (77.8)	30/43 (69.8)	1.00
Surgical therapy, *n* (%)	4/9 (44.4)	26/43 (60.5)	0.47
Persistent bacteremia, *n* (%)	0/6 (0.0)	9/41 (22.0)	0.32
Time to clearance of bacteremia, days, median (IQR)	2.0 (1.5–3.0)	3.0 (1.5–5.0)	0.33
Length of hospital stay in survivors, days, median (IQR)	17.5 (13.5–19.5)	31.0 (19.0–50.0)	**0.02**
In-hospital mortality, *n* (%)	1/9 (11.1)	6/43 (14.0)	1.00
6-mo mortality, *n* (%)	1/8 (12.5)	9/34 (26.5)	0.65

[a] Only percentages less than 1% are carried to the first decimal place. i.v., intravenous. Statistically significant associations are presented in boldface.

following combinations were used: daptomycin-fosfomycin for *S. aureus* IE ($n = 2$; 1 MSSA IE and 1 MRSA IE), daptomycin-rifampin for MRSA IE ($n = 2$), daptomycin-levofloxacin for MRSA IE ($n = 1$), daptomycin–penicillinase-resistant penicillin ($n = 2$; 1 CoNS IE and 1 MSSA IE), and daptomycin-ampicillin for *E. faecalis* IE ($n = 2$).

DISCUSSION

The rising problem of both drug resistance and treatment failures has increased the importance of daptomycin as an alternative therapeutic option for serious Gram-positive infections. Since 2006, "off-label" daptomycin use has frequently extended beyond the indications defined by the FDA (e.g., left-sided *S. aureus* IE and IE due to pathogens such as CoNS, enterococci, and oral streptococci). Although such use has been cited in case reports and small case series (6–9, 13–16), the current investigation is the first multicenter prospective observational study to evaluate patterns of use and outcomes associated with daptomycin for left-sided IE due to major Gram-positive IE pathogens.

This study demonstrated that there was significant clinical use of daptomycin in Gram-positive IE over a wide geographic catchment area. Daptomycin was used in 28.0%, 20.0%, and 17.3% of MRSA, CoNS, and *E. faecalis* IE cases that fulfilled study criteria, respectively. In addition, this study shows that the current SOC therapy for Gram-positive IE was ineffective in 21.4% of cases and associated with intolerable antibiotic-related adverse effects in another 14.3% (Table 7).

In this study, in-hospital and 6-month mortality rates were similar among patients treated with daptomycin and SOC antibiotics in the setting of *S. aureus* (both MSSA and MRSA), CoNS, and *E. faecalis* IE. The outcomes observed with the use of daptomycin are also notable because patients in cohort A (daptomycin cohort) were characterized by higher rates of comorbidities (i.e., diabetes), and daptomycin was the second-line treatment for two-thirds of the subjects in cohort A. Furthermore, over 20% of the patients receiving daptomycin had discontinued a previous antibiotic regimen because of either clinical or microbiological failure. In contrast, no patients discontinued daptomycin because of persistently positive blood cultures or other evidence of clinical or microbiological failure.

Although the sample size is small, the most striking difference in outcome between the daptomycin and SOC antibiotic groups was seen in patients with MRSA IE where daptomycin was associated with significantly faster clearance of bacteremia and shorter LOS. Patients with MRSA IE who received daptomycin also had a numerically lower mortality rate (both in-hospital and 6-month mortalities) than those treated with SOC antimicrobials, although this did not reach statistical significance. We hypothesize that these findings are at least partly due to a faster bactericidal effect of daptomycin than the SOC comparator, vancomycin, which is known for its "slow bactericidal" effect *in vitro* (23, 24) and substantial clinical failure rate *in vivo* (25). Interestingly, the time to clearance of bacteremia for MRSA IE in this study (median and interquartile range, 1 day [range, 1.0 to 2.0 days]) was shorter than the time to clearance of bacteremia in the recent randomized clinical trial of daptomycin use in *S. aureus* bacteremia (mean, 8 days) (8). The reasons for this observation are unclear, but they are likely a combination of the higher doses of daptomycin used in the current study (given daptomycin's concentration-dependent activity), better surgical management of metastatic infectious foci, and/or expertise in treating IE among the ICE centers.

None of the patients who were switched from vancomycin to daptomycin had a MRSA strain with decreased susceptibility to vancomycin (e.g., VISA strains). Given the association between decreased susceptibility to vancomycin and decreased susceptibility to daptomycin in MRSA isolates, the absence of strains with decreased susceptibility to vancomycin in our cohort reduced the likelihood of a subsequent failure of daptomycin treatment. It is important to note that a higher frequency of daptomycin MICs rising above the susceptibility breakpoint has been reported among MRSA VISA strains than among those with lower vancomycin MICs; moreover, hetero-VISA (hVISA) strains have been associated with the develop-

TABLE 5 Univariate analysis of clinical characteristics of Gram-positive infective endocarditis (*S. aureus*, CoNS, and *E. faecalis*) and their association with in-hospital and 6-month mortality[a]

Parameter	In-hospital mortality			6-mo mortality		
	No ($n = 125$)	Yes ($n = 52$)	*P* value	No ($n = 74$)	Yes ($n = 61$)	*P* value
Baseline characteristics						
Age > 60 yrs	62/124 (50.0)	39/52 (75.0)	**<0.01**	36/74 (48.7)	44/60 (73.3)	**<0.01**
Male, *n* (%)	85/123 (69.1)	30/52 (57.7)	0.17	54/74 (73.0)	36/61 (59.0)	0.09
Moderate-severe renal disease, *n* (%)	16/125 (12.8)	15/49 (30.6)	**<0.01**	8/74 (10.8)	16/61 (26.2)	**0.02**
Dialysis, *n* (%)	8/53 (15.1)	7/24 (29.2)	0.21	6/74 (8.1)	7/61 (11.5)	0.51
Diabetes, *n* (%)	34/123 (27.6)	22/50 (40.0)	**0.04**	18/74 (24.3)	25/61 (41.0)	**0.04**
Chronic pulmonary disease, *n* (%)	25/125 (20.0)	11/51 (21.6)	0.84	16/74 (21.6)	12/61 (19.7)	0.78
History of coronary artery disease, *n* (%)	24/121 (19.8)	15/52 (28.9)	0.23	17/74 (23.0)	15/61 (24.6)	0.83
Moderate/severe liver disease, *n* (%)	3/124 (2.4)	4/50 (8.0)	0.11	1/74 (1.4)	6/61 (9.8)	**0.05**
Connective tissue disease, *n* (%)	6/125 (4.8)	2/51 (3.9)	1.00	2/74 (2.7)	3/61 (4.9)	0.66
Chronic immunosuppressive therapy, *n* (%)	7/125 (5.6)	2/51 (3.9)	1.00	1/74 (1.4)	4/61 (6.6)	0.18
Cancer, *n* (%)	16/124 (12.9)	7/51 (13.7)	1.00	11/74 (14.9)	9/61 (14.8)	1.00
Cohort A, *n* (%)	21/125 (16.8)	8/52 (15.4)	0.82	10/74 (13.5)	10/61 (16.4)	0.64
History of i.v. drug use, *n* (%)	8/123 (6.5)	2/51 (3.9)	0.73	6/74 (8.1)	2/61 (3.3)	0.29
Predisposing conditions						
Previous IE, *n* (%)	14/124 (11.3)	2/49 (4.1)	0.24	8/74 (10.8)	3/61 (4.9)	0.34
Congenital heart disease, *n* (%)	11/123 (8.9)	2/50 (4.0)	0.35	8/74 (10.8)	3/61 (4.9)	0.34
History of rheumatic valve, *n* (%)	8/120 (6.7)	7/48 (14.6)	0.13	6/74 (8.1)	7/61 (11.5)	0.51
Native valve predisposition, *n* (%)	46/113 (40.7)	15/48 (31.3)	0.26	29/74 (39.2)	17/61 (27.9)	0.17
IE type						
Native-valve IE, *n* (%)	83/123 (67.5)	34/51 (66.7)	1.00	49/73 (67.1)	40/59 (67.8)	0.93
Prosthetic-valve IE, *n* (%)	40/123 (32.5)	17/52 (33.3)	1.00	24/73 (32.9)	19/59 (32.2)	0.93
Complications and management data						
Stroke, *n* (%)	27/124 (21.8)	14/48 (29.2)	0.32	17/74 (23.0)	17/61 (27.9)	0.51
Embolization, nonstroke, *n* (%)	43/124 (34.7)	12/48 (25.0)	0.22	31/74 (41.9)	15/61 (24.6)	**0.04**
Recurrent embolization, *n* (%)	5/120 (4.2)	5/46 (10.9)	0.14	2/74 (2.7)	6/61 (9.8)	0.14
Intracardiac complications, *n* (%)	51/125 (40.8)	18/52 (34.6)	0.50	31/74 (41.9)	22/61 (36.1)	0.49
New or worsening heart failure, *n* (%)	39/123 (31.7)	23/50 (46.0)	0.08	28/74 (37.8)	23/61 (37.7)	0.99
New conduction abnormalities, *n* (%)	12/124 (9.7)	7/50 (14.0)	0.43	8/74 (10.8)	8/61 (13.1)	0.68
Persistent bacteremia, *n* (%)	24/116 (20.7)	14/44 (31.8)	0.14	17/74 (23.0)	15/61 (24.6)	0.83
Surgical indication, *n* (%)	91/125 (72.8)	47/52 (90.4)	**<0.01**	55/74 (74.3)	51/61 (83.6)	0.19
Surgical therapy, *n* (%)	67/123 (54.5)	23/52 (44.2)	0.25	39/74 (52.7)	24/61 (39.4)	0.12

[a] Only percentages less than 1% are carried to the first decimal place. i.v., intravenous. Statistically significant associations are presented in boldface.

ment of daptomycin heteroresistance (26–28). Thus, the outcomes observed with daptomycin use in this study may not be generalizable to patients with IE due to VISA or hVISA MRSA.

Adverse events associated with daptomycin use, such as elevation in CPK, neuropathies, and eosinophilic pneumonia, were uncommon in our investigation. This finding correlates with our own clinical experience and with other reports (9, 13, 16) but must be interpreted in light of the small sample size of this study. Nevertheless, the absence of a substantive increase in adverse events among patients treated with higher daptomycin doses (≥8 mg/kg/day) calls for a reevaluation of the recommended dosage of daptomycin in the setting of IE, especially in left-sided IE (29).

TABLE 6 Log-binomial model to evaluate risk factors for in-hospital and 6-month mortality among patients with Gram-positive (*S. aureus*, CoNS, and *E. faecalis*) infective endocarditis[a]

Mortality	Patient characteristic	RR (95% CI)	*P* value
In hospital	Age, ≥60 yrs	**2.2 (1.3–3.8)**	**<0.01**
	Diabetes	1.4 (0.9–2.2)	0.14
	Moderate/severe renal disease	**2.1 (1.4–3.2)**	**<0.01**
	Surgical indication	**2.4 (1.1–4.9)**	**0.02**
	Cohort A	0.8 (0.4–1.3)	0.35
6 mo	Age, ≥60 yrs	1.5 (0.9–2.5)	0.05
	Diabetes	1.2 (0.9–1.3)	0.30
	Moderate/severe renal disease	1.5 (1.0–1.6)	0.05
	Moderate/severe liver disease	**1.7 (1.3–1.9)**	**0.03**
	Embolization other than stroke	0.9 (0.7–1.1)	0.45
	Cohort A	1.0 (0.9–1.1)	1.00

[a] Statistically significant associations are presented in boldface.

This study has several noteworthy limitations. The relatively small number of patients in the daptomycin treatment group in this study limits our ability to detect significant differences between groups. Since this is an observational cohort study, we cannot make any definitive inferences between daptomycin dose strategies and patient outcomes. Data for this study were derived from sites in the ICE collaboration, which are mostly tertiary care centers with extensive expertise in IE; therefore, the results of this study may be subject to "center bias." Finally, our study lacked detailed information about tolerability of the antibiotic regimens in the SOC group.

In conclusion, our findings suggest that higher-dose daptomycin may be a valid alternative to SOC antibiotics in the treatment of left-

TABLE 7 Patterns of antibiotic use among patients treated with daptomycin (cohort A)[a]

Parameter	Overall ($n = 29$)	*S. aureus* IE ($n = 12$)	CoNS IE ($n = 8$)	*E. faecalis* IE ($n = 9$)	*P* value
Drug dosage (mg/kg/day), median (IQR)	9.2 (7.7–10.0)	9.6 (8.4–10.5)	9.0 (8.6–9.5)	8.3 (7.1–9.4)	0.47
Duration of therapy, days, median (IQR)	39.0 (25.0–43.0)	42.0 (39.0–44.0)	28.5 (26.0–36.0)	28.5 (22.0–42.5)	0.17
Time to clearance of bacteremia, days, median (IQR)	2.0 (1.0–3.0)	1.5 (1.0–2.0)	3.0 (1.0–5.0)	2.0 (1.5–3.0)	0.58
Length of hospital stay in survivors, days, median (IQR)	20.0 (17.0–46.0)	46.0 (19.0–53.0)	26.0 (22.5–50.0)	17.5 (13.5–19.5)	0.05
Change to daptomycin, *n* (%)	19/28 (67.9)	7/12 (58.3)	6/7 (85.7)	6/9 (66.7)	0.52
Reason for switch to daptomycin					
Clinical failure, *n* (%)	3/28 (10.7)	1/12 (8.3)	1/7 (14.3)	1/9 (11.1)	1.00
Persistent positive blood cultures, *n* (%)	3/28 (10.7)	0/12 (0.0)	3/7 (42.9)	0/9 (0.0)	**0.01**
Adverse events, *n* (%)	4/28 (14.3)	3/12 (25.0)	1/7 (14.3)	0/9 (0.0)	0.33
Other, *n* (%)	9/28 (32.1)	3/12 (25.0)	1/7 (14.3)	5/9 (55.6)	0.24
Discontinuation of daptomycin, *n* (%)	4/28 (14.3)	3/12 (25.0)	0/7 (0.0)	1/9 (11.1)	0.42
Reason for discontinuation of daptomycin					
Clinical failure, *n* (%)	0/28 (0.0)	0/12 (0.0)	0/7 (0.0)	0/9 (0.0)	
Persistent positive blood cultures, *n* (%)	0/28 (0.0)	0/12 (0.0)	0/7 (0.0)	0/9 (0.0)	
Adverse events, *n* (%)	2/28 (7.1)	1/12 (8.3)	0/7 (0.0)	1/9 (11.1)	1.00
Other, *n* (%)	2/28 (7.1)	2/12 (16.7)	0/7 (0.0)	0/9 (0.0)	0.49
Adverse events					
CPK elevation, *n* (%)	1/28 (3.6)	1/12 (8.3)	0/7 (0.0)	0/9 (0.0)	1.00
Nervous system disorders, *n* (%)	2/28 (7.1)	2/12 (16.7)	0/7 (0.0)	0/9 (0.0)	0.49
Eosinophilic pneumonia, *n* (%)	0/28 (0.0)	0/12 (0.0)	0/7 (0.0)	0/9 (0.0)	
Adverse events, total	3/28 (10.7)	3/12 (25.0)	0/7 (0.0)	0/9 (0.0)	0.16

[a] Only percentages less than 1% are carried to the first decimal place. Statistically significant associations are presented in boldface.

sided IE due to susceptible strains of *S. aureus*, CoNS, and *E. faecalis*. Although the present study shows that daptomycin achieved favorable clinical outcomes in a difficult-to-treat subset of patients, further studies are needed to validate our findings and to determine the role of daptomycin in this specific subgroup of IE patients.

TABLE 8 Antibiotic-specific outcomes among patients treated with daptomycin according to daptomycin dosage

Parameter	Daptomycin dosage (mg/kg/day)		*P* value
	<8 ($n = 7$)	≥8 ($n = 19$)	
Adverse events, *n* (%)	0/7 (0.0)	3/19 (15.8)	0.54
CPK elevations, *n* (%)	0/7 (0.0)	1/19 (5.3)	1.00
Nervous system disorders, *n* (%)	0/7 (0.0)	2/19 (10.5)	1.00
Eosinophilic pneumonia, *n* (%)	0/7 (0.0)	0/19 (0.0)	
Time to clearance of bacteremia, days, median (IQR)	1.5 (1.0–3.0)	2.0 (1.0–5.0)	0.47
Duration of therapy in survivors, days, median (IQR)	42.0 (42.0–43.0)	31.0 (23.0–43.0)	0.21
Length of hospital stay in survivors, days, median (IQR)	18.0 (17.0–20.0)	20.0 (17.0–46.0)	0.46
Clinical failure, *n* (%)	0/7 (0.0)	0/19 (0.0)	
Persistent positive blood cultures, *n* (%)	0/7 (0.0)	0/19 (0.0)	
In-hospital mortality, *n* (%)	2/7 (28.6)	5/19 (26.3)	1.00
6-mo mortality	2/6 (33.3)	7/12 (58.3)	0.62

[a] Only percentages less than 1% are carried to the first decimal place. Statistically significant associations are presented in boldface.

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