

Multicenter Study of High-Dose Daptomycin for Treatment of Enterococcal Infections

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Enterococci are among the leading pathogens isolated in hospital-acquired infections. Current antimicrobial options for vancomycin-resistant enterococci (VRE) are limited. Prior data suggest that daptomycin at >6 mg/kg of body weight/day may be used to treat enterococcal infections. We retrospectively evaluated the effectiveness and safety of high-dose daptomycin (HD-daptomycin) therapy (>6 mg/kg) in a multicenter cohort of adult patients with enterococcal infections to describe the characteristics and outcomes. Two hundred forty-five patients were evaluated. *Enterococcus faecium* was identified in 175 (71%), followed by *Enterococcus faecalis* in 49 (20%) and *Enterococcus* spp. in 21 (9%); overall, 204 (83%) isolates were VRE. Enterococcal infections included bacteremia (173, 71%) and intra-abdominal (35, 14%) and bone and joint (25, 10%) infections. The median dosage and duration of HD-daptomycin were 8.2 mg/kg/day (interquartile range [IQR], 7.7 to 9.7) and 10 days (IQR, 6 to 15), respectively. The overall clinical success rate was 89% (193/218), and microbiological eradication was observed in 93% (177/191) of patients. The median time to clearance of blood cultures on HD-daptomycin was 3 days (IQR, 2 to 5). The 30-day all-cause mortality rate was 27%, and 5 (2%) patients developed daptomycin-nonsusceptible enterococcal strains while on HD-daptomycin. Seven patients (3%) had creatine phosphokinase (CPK) elevation, yet no HD-daptomycin regimen was discontinued due to an elevated CPK and all patients were asymptomatic. Overall, there was a high frequency of clinical success and microbiological eradication in patients treated with HD-daptomycin for enterococcal infections, even in patients with complicated and difficult-to-treat infections. No adverse event-related discontinuation of HD-daptomycin was noted. HD-daptomycin may be an option for the treatment of enterococcal infections.

Infections with multidrug-resistant Gram-positive organisms are becoming highly prevalent (1). In particular, vancomycin-resistant enterococcus (VRE) infections are difficult to treat and have been associated with multiple patient comorbidities and prolonged duration of hospitalization, with the predominant pathogens being *Enterococcus faecalis* and *Enterococcus faecium* (2, 3). In fact, *Enterococcus* spp. are the second most common nosocomial bloodstream pathogens isolated in the United States (4), with VRE frequencies in intensive care units (ICU) exceeding 30% (5). Unfortunately, there are limited effective therapeutic options for VRE infections.

Currently, linezolid is approved by the U.S. Food and Drug Administration (FDA) for the treatment of VRE infections; however, several limitations exist with this agent (6). Studies evaluating linezolid for the treatment of vancomycin-resistant *E. faecium* bloodstream infection (BSI) have revealed clinical success frequencies ranging from 58% to 78% (7, 8). However, reports of linezolid resistance in VRE have emerged, with an incidence as high as 20% (9). Moreover, prolonged treatment with linezolid can lead to myelosuppression, including neutropenia, thrombocytopenia, and anemia, which are frequent comorbid conditions

already present in many patients with VRE infections (6, 10). Lastly, linezolid is bacteriostatic against enterococci (6), and in serious infections (e.g., prolonged VRE bacteremia, specifically endocarditis), a bactericidal agent is preferred (11).

Daptomycin is a concentration-dependent bactericidal agent currently approved at 4 and 6 mg/kg of body weight daily for the treatment of skin and skin structure infections (SSSIs) and *Staphylococcus aureus* bacteremia, respectively (12, 13). Both *in vivo* and *in vitro* studies have revealed that using higher dosages of daptomycin increased both the degree and speed of bactericidal activity due to its concentration-dependent pharmacodynamic mecha-

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nism. Further, high dosages can decrease the emergence of resistance in *Staphylococcus aureus* (14). Daptomycin possesses similar and potent activity against enterococci and is FDA approved for the treatment of SSSIs, including those caused by vancomycin-susceptible *E. faecalis* (15). However, due to intrinsically lower susceptibility in enterococci than in staphylococci, MICs tend to be 2 mg/liter, suggesting that larger doses of daptomycin (approximately 8 mg/kg daily) may be necessary to obtain kill ratios similar to those for staphylococci (16). Currently, there are no clinical dosing recommendations for the use of daptomycin against enterococci, and most dosages reported via case reports indicate that a median dose of 6 mg/kg is most frequently used (17, 18). The emergence of resistance in enterococci to daptomycin has been reported; notably, these patients have had complicated infections (e.g., osteomyelitis, medical device infections, and endocarditis) and have been treated with daptomycin at doses of 6 mg/kg or less (19).

Several case reports, registries, and small-cohort studies have observed positive clinical outcomes and have suggested the use of higher doses of daptomycin for enterococcal infections (20–23). Gallagher and colleagues performed a retrospective analysis of patients with VRE BSI treated with daptomycin and concluded that clinical success was associated with a daptomycin dose of ≥ 6 mg/kg (adjusted odds ratio [aOR], 7.29, 95%; confidence interval [CI], 1.02 to 52.0) (24). It is possible that higher dosages of daptomycin in VRE infections may improve the efficacy of this agent and prevent the emergence of resistance during therapy. Our previous multicenter observational study examining high-dose daptomycin for the treatment of infections caused by Gram-positive organisms suggested that this approach may be both efficacious and safe (21). However, staphylococci were the primary pathogens in that cohort; therefore, a focused evaluation of high-dose daptomycin in serious enterococcal infections was not possible. The objective of the present study was to evaluate the safety and effectiveness of high-dose daptomycin therapy (>6 mg/kg by total body weight) in patients with enterococcal infections in a large multicenter cohort of patients.

(An abstract containing part of this study was accepted for presentation in poster format at the 21st European Congress of Clinical Microbiology and Infectious Diseases [ECCMID] in Milan, Italy, in May 2011 and at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC] in San Francisco, CA, in September 2012.)

MATERIALS AND METHODS

A multicenter, retrospective cohort was conducted from January 2005 to October 2012 and included adult patients treated with daptomycin at doses of >6 mg/kg (total body weight) and with documented infection with enterococci. The study population included patients ≥ 18 years of age with enterococcal infections at any site who received daptomycin at >6 mg/kg per dose for at least 3 consecutive days (≥ 72 h). Patients were excluded if they had a diagnosis of pneumonia or urinary tract infection in the absence of enterococcal bacteremia or received any form of dialysis (e.g., hemodialysis, continuous ambulatory peritoneal dialysis, and continuous renal replacement therapy). Data were collected retrospectively using a standardized, electronic tool to capture demographics (e.g., age, gender, weight, and renal function), infection site, diagnosis, severity of illness at the initiation of high-dose daptomycin therapy as determined by APACHE II score, comorbid conditions, prior and concomitant antimicrobial use, surgical procedures within the previous 30 days, duration of therapy, length of hospital stay, 30-day mortality, and overall clinical out-

come as ascertained by the treating medical team. Safety data were also collected using adverse-event reporting in the medical record.

Clinical assessments were determined at the end of daptomycin therapy. Safety and adverse events were evaluated for all patients, while effectiveness was determined only for patients with adequate medical record documentation to determine clinical response. Clinical outcomes were characterized as follows: cure, clinical signs and symptoms resolved and/or no additional antibiotic therapy necessary, or infection cleared with negative cultures reported at the end of daptomycin therapy; improved, partial resolution of clinical signs and symptoms and no additional antibiotic therapy necessary at the end of daptomycin therapy; and failure, inadequate response to daptomycin therapy or resistant, worsening, or new/recurrent signs and symptoms or a positive culture reported at the end of therapy (20–22, 25). Patients with nonevaluable outcomes were those for whom medical records did not contain all necessary information to determine response at the end of inpatient daptomycin therapy. Additional clinical assessments included the presence and duration of the following: fever (temperature $\geq 38.3^{\circ}\text{C}$), leukocytosis (≥ 10 cells/ mm^3), ICU admission, mechanical ventilation, positive blood culture (time from first positive blood culture to first day of 48 h of negative cultures), and site(s) of infection determined by the diagnosing practitioner's discretion, with the exception of specific definitions for endocarditis (26), osteomyelitis (27), and uncomplicated and complicated bacteremia (13) (see the supplemental material for further details). Duration of bacteremia was calculated as the number of days between the first positive blood culture and the first negative blood culture result.

Microbiological assessment. Microbiological data were obtained from available culture data during hospitalization, except for patients with osteomyelitis for whom culture data may include those from outpatient clinic visits, if available. Microbiological response was defined as organism eradication, organism persistence, or no follow-up culture data available. Eradication was defined as elimination of the organism while on high-dose daptomycin, and persistence was defined as failure to eradicate the organism at the end of high-dose daptomycin therapy (21, 25). Organism identification, local susceptibility data, and baseline blood isolates were collected, if available, and evaluated for extended microbiological assessment and verification at a central research laboratory facility (Anti-Infective Research Laboratory, Wayne State University). For these isolates, daptomycin and vancomycin susceptibility testing was performed by broth microdilution (BMD) and by Etest according to Clinical and Laboratory Standards Institute guidelines and the manufacturer's instructions (bioMérieux, Durham, NC) (28), respectively. If the isolate was not available, the susceptibility interpretation and methodology were recorded from the referring institution.

Safety assessment. All adverse events, including serious adverse events, were evaluated for all subjects who received at least one dose of daptomycin therapy. Adverse events were recorded only if a direct causal relationship to daptomycin was suspected and documented in the patient's medical chart by the primary team. Creatine phosphokinase (CPK) levels were assessed by evaluating any abnormal value or change from baseline, if available. CPK elevation was defined in previous literature based on 2 sequential measurements during the period after 3 doses to 3 days after therapy (29). Patients with unexplained signs and symptoms of myopathy in conjunction with a CPK elevation of $\geq 1,000$ IU/liter ($\sim 5\times$ the upper limit of normal [ULN]) or asymptomatic patients with a CPK of $\geq 2,000$ IU/liter ($\geq 10\times$ the ULN) were reported in further detail (15).

Statistical analysis. SPSS Statistics, version 20.0 (IBM SPSS Inc., Chicago, IL), was used to perform descriptive statistics, including data frequencies and distributions for categorical data and median and interquartile range (IQR) for continuous data. Daptomycin dose and maximum observed CPK levels were analyzed for relationship by using the Spearman's rank correlation. In addition, various MIC testing methods (automated institutional MIC versus BMD and Etest) were analyzed for relationship by using Spearman's rank correlation. Clinical outcome was

TABLE 1 Baseline demographic and clinical characteristics

Characteristics of patients (n = 245)	Median (IQR) or n (%)
Age, yr	58 (49–65)
APACHE II score	9 (6–14)
Weight, kg	76.2 (61.3–93.2)
Creatinine clearance	69 (43.6–97.3)
Male	131 (53.5)
Prior hospitalization	207 (84.5)
Prior surgery	53 (23.3)
Neutropenia	51 (20.8)
Diabetes	87 (35.5)
Renal disease	48 (19.6)
Liver disease	38 (15.5)
Solid organ/bone marrow transplantation	48 (19.6)
Chemotherapy and/or radiation	53 (21.6)
ICU admission	125 (51)
Mechanical ventilation	85 (34.7)
Antibiotic exposure prior to admission	
Prior vancomycin	108 (44.1)
Prior daptomycin	13 (5.3)
Prior linezolid	32 (13.1)
Antibiotics given before high-dose daptomycin ^a	
Linezolid	57 (23.3)
Vancomycin ^b	25 (10.2)
Low-dose daptomycin (≤ 6 mg/kg)	11 (4.5)
Quinupristin-dalfopristin	5 (2.0)
Tigecycline	3 (1.2)
Types of infections	
Intra-abdominal	35 (14.3)
Bone or joint	25 (10.2)
Skin or wound	11 (4.5)
Meningitis	1 (0.4)
Bloodstream infection	173 (70.6)
i.v. catheter	66 (38.2)
Endocarditis	15 (8.7)
Intra-abdominal	32 (18.5)
Skin or wound	13 (7.5)
Urinary	10 (5.8)
Bone or joint	5 (2.9)
Prosthetic device	5 (2.9)
Unknown	27 (15.6)

^a Antibiotic given during hospitalization of enterococcal infection that has *in vitro* activity against enterococci.

^b Evaluated in vancomycin-susceptible enterococci.

compared by Pearson's chi-square in relation to daptomycin MIC groups (≤ 2 mg/liter versus > 2 mg/liter).

RESULTS

A total of 245 patients with enterococcal infections received high-dose daptomycin during the time period studied. Demographic and clinical characteristics of the patients are presented in Table 1. A total of 173 patients (70.6%) had a positive blood culture. Among BSI patients, 97 (56.1%) had complicated bacteremia and 76 (43.9%) had uncomplicated bacteremia. Concomitant site of BSI along with the other types of infections are displayed in Table 1. Two hundred twenty-one (90.2%) patients were given at least one antimicrobial prior to the receipt of high-dose daptomycin for enterococcal infections, and the median time to switch to high-dose daptomycin was 4 days (IQR, 2 to 6.5). The median dose and

TABLE 2 Baseline vancomycin and daptomycin MICs

Organism and vancomycin MIC (mg/liter)	Daptomycin MIC (mg/liter)								
	0.25	0.38	0.5	1.0	1.5	2.0	3.0	4.0	8.0
<i>Enterococcus faecium</i>									
≤ 4				1	1			1	
8–16							1	2	
≥ 32				8	6	38	11	53	1
<i>Enterococcus faecalis</i>									
≤ 4			1	2		1			
8–16									
≥ 32	1	1	1	3	4	4		2	
<i>Enterococcus</i> spp.									
≤ 4			1						
8–16								1	
≥ 32	1			1	2	1	2	3	
Total (n = 155)	2	1	3	15	13	44	14	62	1

hospital duration of high-dose daptomycin were 8.2 mg/kg (IQR, 7.7 to 9.7) and 10 days (IQR, 6 to 15), respectively. One hundred sixty-eight (68.6%) patients had doses of ≥ 8 mg/kg; 34 of these (13.9%) patients were dosed with ≥ 10 mg/kg. Two hundred fourteen (87.3%) patients received daptomycin every 24 h. Within our whole cohort, 43.7% (107/245) of patients were given another antibiotic concomitantly with daptomycin. The most common type of antibiotic administered concomitantly with high-dose daptomycin was a beta-lactam agent (76.6%, 82/107), specifically a carbapenem (39%; 32/82). Most of these patients were given a beta-lactam, as their infections also involved a Gram-negative pathogen (62.6%; 67/107) along with the enterococcus.

The organisms isolated in 245 patients were *E. faecium*, *E. faecalis*, and *Enterococcus* spp., in 175 (71.4%), 49 (20%), and 21 (8.6%), respectively. Of these enterococci, 204 (83.3%) were vancomycin resistant according to institutional automated MIC testing methods. MICs of vancomycin are displayed in Table 2. One hundred fifty-five (63.3%) isolates had daptomycin susceptibility available from the medical charts. The MIC₅₀ and MIC₉₀ of daptomycin for baseline enterococcal isolates were 2 mg/liter and 4 mg/liter, respectively (see Table 2 for the frequency and distribution of institutional daptomycin MICs). Seventy-five enterococcal strains were recovered for extended microbiological assessment with BMD and Etest for vancomycin and daptomycin susceptibility. Thirty-seven (49.3%) isolates were *E. faecium*, 29 (38.7%) were *E. faecalis*, and 9 (12%) were *Enterococcus* spp. Overall, 56 (74.6%) were VRE as confirmed by both BMD and Etest. The MIC₅₀ and MIC₉₀ of daptomycin for these 75 enterococcal isolates by both BMD and Etest were 1 mg/liter and 2 mg/liter, respectively. The median daptomycin MICs for *E. faecium* by BMD and Etest were 2 mg/liter (range of 0.25 to 4 mg/liter) and 2 mg/liter (range of 0.5 to 4 mg/liter), respectively. *E. faecalis* median daptomycin MICs by BMD and Etest were 0.5 mg/liter (range, 0.125 to 2 mg/liter) and 1 mg/liter (range, 0.25 to 3 mg/liter), respectively. The median daptomycin MIC for *Enterococcus* spp. by BMD and Etest were 1 mg/liter (range, 0.5 to 2 mg/liter) and 1.5 mg/liter (range, 0.5 to 3 mg/liter), respectively. Thirty-one enterococcal isolates had a reported daptomycin MIC from the institution, and a correlation of daptomycin BMD and Etest method was observed, with Spearman's rank correlation coefficients of 0.53 ($P = 0.002$) and 0.42 ($P = 0.019$), respectively.

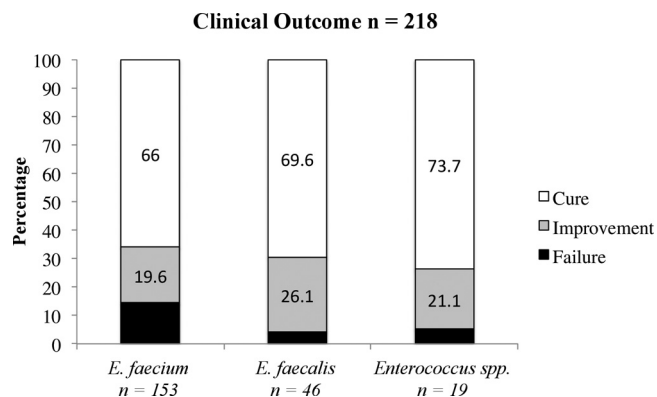


FIG 1 Clinical outcome proportion per enterococcal species. Individual percentage of clinical success component is reported within the stacked bars per enterococcal species. The frequency of clinical success for *E. faecium*, *E. faecalis*, and *Enterococcus* spp. were 85.6%, 95.7%, and 94.7%, respectively.

Two hundred eighteen (89%) patients were clinically evaluable; 147 (67.4%) patients were cured and 46 (21.1%) improved from their enterococcal infection. Clinical success (21, 22) was evaluated as the combined total of patients cured or improved; overall, a total of 193 (88.5%) patients achieved clinical success. The proportion of clinical success by enterococcal species is described in Fig. 1, which displays a difference in clinical success for *E. faecium* versus *E. faecalis*. One hundred thirty-seven (62.8%) patients had clinical outcomes available with daptomycin susceptibility. Stratification by daptomycin MIC is displayed in Fig. 2 and demonstrated the variability in outcome as it relates to MIC. Clinical success did not differ between daptomycin MIC groups, with 53.4% and 46.6% for MICs of ≤ 2 mg/liter and > 2 mg/liter, respectively ($P = 0.371$). One hundred ninety-one (78%) patients were microbiologically evaluable since follow-up cultures were available, and overall, 177/191 (92.7%) patients had microbiological eradication with high-dose daptomycin. Of the microbiologically evaluable patients, 32/33 (97%) with *E. faecalis*, 134/147 (91.2%) with *E. faecium*, and 11/11 (100%) with *Enterococcus* spp. had microbiological eradication. The median time to clearance of blood cultures was 3 days (IQR, 2 to 5). Of the 14 patients with microbiological persistence, 10 (71.4%) had complicated bacteremia, including 1 (7.1%) with osteomyelitis, 2 (14.7%) with skin

and wound infection, 5 (35.7%) with intra-abdominal infection, 4 (28.6%) with intravenous (i.v.)-catheter-related infection, 1 (7.1%) with a left ventricular assist device, and 1 (7.1%) with right-sided infective endocarditis. The median durations of fever and leukocytosis during the enterococcal infection were 3 days (IQR, 1 to 6) and 7 days (IQR, 2 to 14.3), respectively. The median ICU length of stay and total length of stay were 8 days (IQR, 3 to 15) and 22 days (IQR, 13 to 39), respectively. Among the patients admitted to the ICU, 85/125 (68%) were mechanically ventilated; the median duration of mechanical ventilation was 8 days (IQR, 2 to 14). The all-cause in-hospital mortality rate was 19.6% (48/245) of patients. Of these patients, 42/48 (87.5%) had *E. faecium* isolated, 46/48 (95.8%) had VRE isolated, and 41/48 (85.4%) had BSI. Forty-one of the expired patients were microbiologically evaluable, and 34/41 (82.9%) showed microbiological eradication. The 30-day all-cause mortality rate was 26.5% (50 patients) for the 189 patients (77.1%) who had follow-up.

Overall, no patients experienced an adverse event attributed to high-dose daptomycin therapy. Baseline and subsequent CPK levels were available for 220 (89.8%) patients. Fifty-four (22%) were receiving concomitant 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), and 20 (8.2%) patients were placed on intramuscular injections while on high-dose daptomycin. Seven (3.2%) patients had CPK elevations from baseline; one patient had a baseline CPK greater than or equal to the ULN that increased to $5\times$ the ULN while on high-dose daptomycin, and the remaining six patients had a baseline CPK less than or equal to the ULN that increased to $3\times$ the ULN while on high-dose daptomycin. A distribution of observed maximum CPK level after 3 days of high-dose daptomycin stratified by daptomycin dosages is shown in Fig. 3. No apparent relationship between high-dose daptomycin and maximum CPK level was observed (Spearman's rank correlation coefficient of 0.07; $P = 0.28$). Of interest, one patient who had a baseline CPK level of $\geq 10\times$ the ULN saw a decrease in CPK to a level of 753 IU/liter after 6 days of high-dose daptomycin (10.4 mg/kg every 24 h) and remained asymptomatic throughout therapy. There was no reported myopathy or myositis while on high-dose daptomycin. All patients with CPK levels of $\geq 5\times$ ULN were asymptomatic, and no patients were reported to have a CPK level increase to $\geq 10\times$ the ULN while on daptomycin. High-dose daptomycin was observed in one patient case to be safe up to 15.7

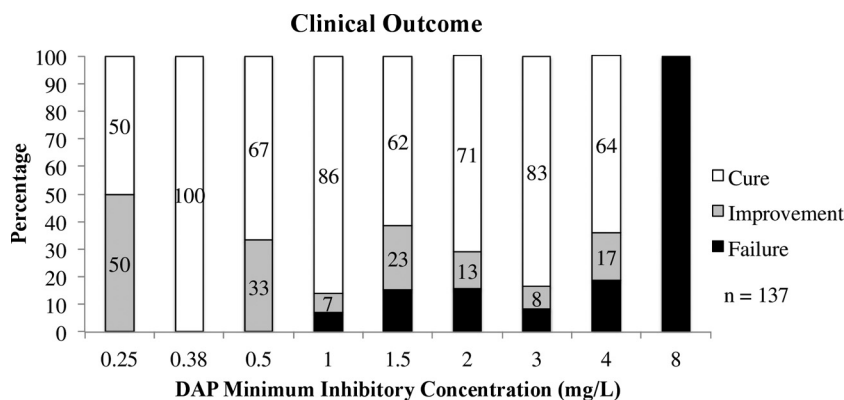


FIG 2 Clinical success stratified by daptomycin (DAP) MIC. The individual percentages of the clinical success component are reported within the stacked bars per daptomycin MIC. The frequencies of clinical success for daptomycin MICs of 0.25, 0.38, 0.5, 1.0, 1.5, 2, 3, 4, and 8 mg/liter were 100%, 100%, 100%, 93%, 85%, 84%, 91%, 81%, and 0%, respectively.

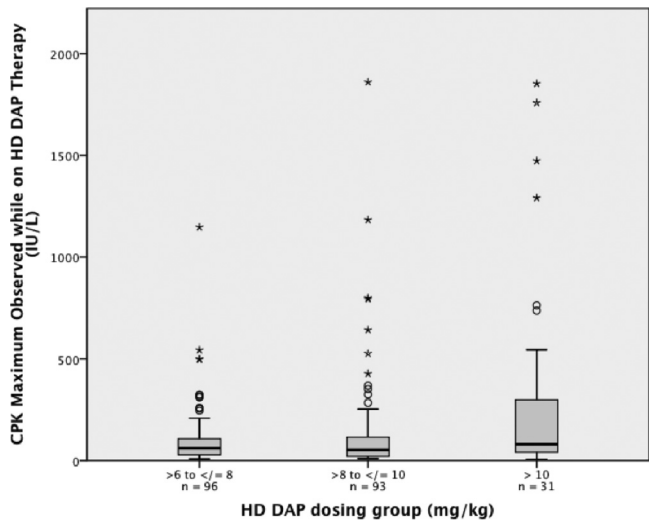


FIG 3 Box-and-whisker plot of maximum observed creatine phosphokinase level after 3 doses to 3 days of high-dose daptomycin (HD DAP) Circles indicate outliers and asterisks indicate extreme values.

mg/kg (every 24 h) for up to 14 days when used to treat vancomycin-resistant *E. faecium* complicated bacteremia from an abdominal source; the highest CPK level observed was 383 IU/liter. The highest observed patient weight was 164 kg; this patient received daptomycin 8.2 mg/kg (every 24 h) for 12 days and with no observation of CPK elevation for the treatment of vancomycin-resistant *E. faecium* infective endocarditis, with the highest CPK level observed at 26 IU/liter.

Daptomycin nonsusceptibility was identified in six patients by the institution’s automated MIC testing system or by Etest methodology; one isolate was found to be nonsusceptible in the initial blood culture, and five strains developed nonsusceptibility during daptomycin therapy. One patient had a vancomycin-resistant *E. faecium* initial daptomycin MIC of 8 mg/liter treated with vancomycin for 3 days and switched to high-dose daptomycin (7.94 mg/kg every 24 h) for right-sided infective endocarditis once VRE was identified. Daptomycin was later switched to linezolid after 7 days of high-dose daptomycin therapy, and blood cultures cleared after 3 days of linezolid therapy (linezolid MIC of 2 mg/liter). Five (2%) patients developed nonsusceptibility to daptomycin, with all isolates being vancomycin-resistant *E. faecium*. These five patients were treated with high-dose daptomycin; infection, daptomycin

dosages, MIC data, and outcome are described in Table 3. None of these patients were given a beta-lactam concomitantly with high-dose daptomycin.

DISCUSSION

This study is the largest evaluation of a cohort of patients treated with high-dose daptomycin for enterococcal infections. Our patient population demographics were very similar to those of prior studies evaluating enterococcal infections, specifically with VRE, in parameters such as ICU admission, previous vancomycin use, mechanical ventilation, and malignancy (30, 31). Within our cohort, 91 (37.1%) patients were switched to high-dose daptomycin following prior therapy with *in vitro* activity (e.g., linezolid for VRE or vancomycin for vancomycin-susceptible enterococci); 82 (33.5%) were administered high-dose daptomycin as a second-line agent, and 9 (3.7%) were provided high dose daptomycin as a third-line agent. The majority was initially treated with high-dose daptomycin for enterococcal infections that was associated with a high frequency of clinical success similar to what has been reported in previous literature regarding the use of high-dose daptomycin (20, 21). A subgroup analysis of our data revealed that enterococcal BSI patients had a higher percentage of severe complicated infections such as infective endocarditis and intra-abdominal infections than in previous publications (22, 24). We noted that a higher percentage of patients with enterococcal BSI tended to have comorbid conditions such as transplantation, diabetes, and liver disease (data not shown). We also found that more patients received daptomycin in the ICU than in the Cubicin Outcomes Registry and Experience (CORE) study (53.2% versus 27%) for treatment of enterococcal bacteremia (22). Our data had clinical success frequencies similar to the CORE data (22); in contrast, a higher frequency of microbiological cure (92.7%, 152/164) was observed than in previous literature (21, 24). This improved outcome suggests that a higher dose of daptomycin may be a favorable treatment option for complicated enterococcal BSI, since the median dose of daptomycin for enterococcal BSI in our patients was higher than in the CORE data, 8.2 mg/kg (range, 6.02 to 15.70 mg/kg) and 6 mg/kg (range, 2.9 to 14.8 mg/kg), respectively.

The treatment options for VRE BSI are limited. Although FDA approved for the treatment of VRE infections, including concomitant BSI due to *E. faecium*, linezolid is bacteriostatic (6). A retrospective cohort analysis by Crank and colleagues compared linezolid to daptomycin for VRE BSI and found no statistical difference in mortality (29.4% versus 46.3%; *P* = 0.10) (32). The mortality rate was higher in the daptomycin group studied by

TABLE 3 Patients with vancomycin-resistant *E. faecium* infections that developed nonsusceptibility to daptomycin^a

Infection	Dose of HD-DAP (mg/kg)	Baseline DAP MIC (mg/liter)	No. of days to MIC change while on HD-DAP	Subsequent DAP MIC (mg/liter)	Outcome
Complicated i.v.-catheter-related BSI	8.20	2 ^b	16	>4 ^b	Added gentamicin but expired during hospitalization
Complicated i.v.-catheter-related BSI	8.20	4 ^b	13	>4 ^b	Discharged with HD-DAP with gentamicin DNS identified after DC; NA for 30 days' FU
Complicated prosthetic-device-related BSI	6.17	1 ^b	8	>4 ^b	Switched to LIN and cleared BSI; NA for 30 days' FU
Complicated BSI from skin/wound	10.10	4 ^c	58	32 ^c	Switched to quinupristin-dalfopristin and cleared BSI; alive at 30 days' FU
Intra-abdominal	7.50	2 ^c	13	24 ^c	Switched to LIN and not other FU cultures; alive at 30 days' FU

^a HD-DAP, high-dose daptomycin; DNS, daptomycin nonsusceptibility; DC, discharge from hospital; LIN, linezolid; NA, not available; FU, follow-up.
^b MIC identified by automated testing method from institution.
^c MIC identified by Etest testing methodology.

Crank and colleagues, but there were significant differences between the two treatment groups in baseline characteristics, with a higher proportion of the daptomycin group having shock and having received previous treatment. Our enterococcal BSI hospital mortality rate was 23.7% (41/173), lower than in the retrospective cohort study by Crank and colleagues. In addition, a retrospective study by Mave and colleagues compared the clinical outcomes of linezolid and daptomycin and found no significant difference between the two groups (33). Our study's characteristics were similar to those of the retrospective study by Mave and colleagues (not shown), along with the frequency of mortality in VRE BSI, 27% (40/148) and 26.7% (8/30), respectively. After reviewing all of these factors, the frequency of microbiological cure was found to be much higher in our study than in that by Mave and colleagues for the treatment of VRE BSI with daptomycin. This may suggest that high-dose daptomycin may be a favorable option for the treatment of VRE BSI.

Combination therapy of daptomycin and another antibiotic such as rifampin, gentamicin, linezolid, or a beta-lactam may also be an option for enterococcal infections, especially for severe or refractory VRE BSI (34, 35). Of interest, within our cohort of patients that were concomitantly administered a beta-lactam, 89.1% (41/46) of the VRE BSI patients had clinical success similar to that found in a recent publication (36). This may be of interest, from recent data describing a positive outcome in beta-lactams and daptomycin used in the clearance of refractory VRE bacteremia. It is unknown if the standard dose of daptomycin (6 mg/kg) in combination with a beta-lactam maybe a viable option compared to high-dose daptomycin, but further research is necessary to evaluate the impact of concomitant beta-lactams with daptomycin, especially in serious VRE infections and with various dosages of daptomycin (low versus high dose). Our data may show a high frequency of success, but this was not an *a priori* focus for data collection. Even if these enterococci are resistant to beta-lactams, including ampicillin, beta-lactams appear to enhance the activity of daptomycin through reduction in net positive surface charge (35).

Overall, all patients tolerated high-dose daptomycin, and no adverse events were reported while on daptomycin. CPK levels were obtained in approximately 90% of our patient population. Prior studies have reported high dosages of daptomycin to be safe, with no elevations of CPK concentrations while on therapy (23, 37), although others have reported CPK elevations that led to the discontinuation of high-dose daptomycin due to musculoskeletal symptoms or related adverse events (20, 38, 39). Recent data have shown that high-dose daptomycin may elevate CPK level at an incidence of 2.5 to 8.3% (39), but no patients reported symptoms consistent with muscle toxicity (21, 40). This finding is consistent with our data, demonstrating high-dose daptomycin to be well tolerated. Within our study, the highest daptomycin dose given to a patient was 15.7 mg/kg, and the longest duration of therapy given to another patient was 128 days; these two patients tolerated high-dose daptomycin for a prolonged duration and remained asymptomatic, and neither experienced a CPK elevation. Additional study supports that high-dose daptomycin may be tolerable and does not necessarily have a dose- or duration-dependent relationship to CPK elevation (41).

Our study was a multicenter observational investigation that incorporated a diverse cohort of adult patients across the United States; however, this retrospective design does have some limita-

tions. Our study design is descriptive, and therefore, we were not able to compare our results with those derived from patients receiving lower dosages of daptomycin or another anti-VRE agent such as linezolid. In addition, not all patients had CPK levels collected to evaluate for potential elevation, although it is interesting to note that all patients evaluated were asymptomatic and no patient discontinued therapy while on high-dose daptomycin. On account of this study's retrospective nature, it is difficult to detect other possible adverse events, and there could have been adverse events that were not attributed to daptomycin.

In conclusion, these results suggest that high-dose daptomycin may be an option for the treatment of enterococcal infections, including VRE BSI. This study also suggests that high-dose daptomycin may provide a high frequency of clinical success along with microbiological eradication, despite significant comorbid conditions. Since high-dose daptomycin appears to be a safe, effective, and tolerable treatment option, further prospective studies of high-dose daptomycin for treatment of VRE infections are warranted.

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