9-1-2013

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

Anthony M. Casapao
Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

Ravina Kullar
College of Pharmacy, Oregon State University

Susan L. Davis
Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

Donald P. Levine
School of Medicine, Wayne State University

Jing J. Zhao
Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

See next page for additional authors

Authors
Anthony M. Casapao, Ravina Kullar, Susan L. Davis, Donald P. Levine, Jing J. Zhao, Brian A. Potoski, Debra A. Goff, Christopher W. Crank, John Segreti, George Sakoulas, Sara E. Cosgrove, and Michael J. Rybak

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

ANTHONY M. CASAPAO[1,2], RAVINA KULLAR[3], SUSAN L. DAVIS[2,4], DONALD P. LEVINE[5,6], JING J. ZHAO[2,7], BRIAN A. POTOSKI[8,9], DEBRA A. GOFF[10,11], CHRISTOPHER W. CRANK[12], JOHN SEGRETI[13], GEORGE SAKOULAS[14], SARA E. COSGROVE[15,16], MICHAEL J. RYBAK[1,2,5]

[1] Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Avenue, Detroit, MI 48201, USA
[2] Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Avenue, Detroit, MI 48201, USA
[3] Department of Pharmacy Practice, College of Pharmacy, Oregon State University, Oregon Health Sciences University, Portland, OR 97329, USA
[4] Department of Pharmacy Services, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, USA
[5] Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, MI 48201, USA
[6] Department of Medicine, Division of General Internal Medicine, Detroit Receiving and University Health Center, 4201 St. Antoine, Detroit MI 48201, USA
[7] Department of Pharmacy, Harper University Hospital, Detroit Medical Center, 3990 John R, Detroit, MI 48201, USA
[8] Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh PA 15213, USA
[9] Antibiotic Management Program, University of Pittsburgh Medical Center, Presbyterian University Hospital, 200 Lothrop Street, Pittsburgh, PA 15213, USA
[10] Department of Pharmacy, The Ohio State University Wexner Medical Center, 410 W. 10th Avenue, Columbus, OH 43210, USA
[11] Pharmacy Practice and Administration, The Ohio State University College of Pharmacy, Columbus, OH 43210, USA
[12] Department of Pharmacy, Rush University Medical Center, 1653 W. Congress Parkway, Chicago, IL 60612, USA
[13] Department of Internal Medicine, Rush University Medical Center, 1653 W. Congress Parkway, Chicago, IL 60612, USA
[14] Department of Pediatrics, School of Medicine, University of California San Diego, La Jolla CA 92093, USA
[15] Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
[16] Department of Hospital Epidemiology and Infection Control, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287, USA

Abstract Enterococci are among the leading pathogens isolated in hospital-acquired infections. Current antimicrobial options for vancomycin-resistant enterococci (VRE) are limited. Prior data suggests that daptomycin > 6mg/kg/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 and forty-five patients were evaluated. *Enterococcus faecium* was identified in 175 (71%), followed by 49 (20%) *Enterococcus faecalis* and 21 (9%) *Enterococcus* spp., overall 204 (83%) were VRE. Enterococcal infections included bacteremia (173, 71%), intra-abdominal (35, 14%) and bone/joint (25, 10%). The median dose and duration of HD-daptomycin was 8.2 mg/kg/day (IQR 7.7-9.7) and 10 days (IQR 6-15), respectively. 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 2-5). Thirty-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.

Keywords High dose, daptomycin, enterococcus, *Enterococcus faecium*, bloodstream infection, Creatine phosphokinase

INTRODUCTION

Infections with multidrug-resistant Gram-positive organisms are becoming highly prevalent(1). In particular, vancomycin-resistant enterococci (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 pathogen isolate 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 US 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 VRE *faecium* bloodstream infection (BSI) have revealed clinical success frequency ranging from 58% to 78%(7, 8). However, reports of linezolid resistance have emerged in VRE, 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 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 mechanism. 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 compared to staphylococci, minimum inhibitory concentrations (MIC) tend to be at 2 mg/L suggesting larger doses of daptomycin (approximately 8 mg/kg daily) may be necessary to obtain similar kill ratios to 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, endocarditis) and have been treated with daptomycin at dosages 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 (aOR 7.29, 95%; CI 1.02-52.0)(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 multi-center 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 multi-center cohort of patients.

METHODS

A multi-center, retrospective cohort was conducted from January 2005 to October 2012 and included adult patients treated with daptomycin at dosages 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 > 6 mg/kg per dose for at least 3 consecutive days (≥ 72 hours). 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, 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 outcome as ascertained by the treating medical team. Safety data was 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 in all patients, while effectiveness was only determined in 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; 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 non-evaluable 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 > 38.30 C), leukocytosis (> 10 cells/mm3), ICU admission, mechanical ventilation, positive blood culture (time from 1st positive blood culture to

Table 1
Baseline demographic and clinical characteristics.

Characteristics	Median (IQR) or n (%) n = 245
Age, years	58 (49-65)
APACHE II Score	9 (6-14)
Weight, kilograms	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/BMT	48 (19.6)
Chemotherapy and/or Radiation	53 (21.6)
ICU admission	125 (51)
Mechanical ventilation	85 (34.7)
Antibiotic Exposure Prior Admission	
Prior Vancomycin	108 (44.1)
Prior Daptomycin	13 (5.3)
Prior Linezolid	32 (13.1)
Antibiotics Given Before High-Dose DAP*	
Linezolid	57 (23.3)
Vancomycin$^{\Delta}$	25 (10.2)
Low-Dose Daptomycin (≤ 6mg/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)
IV 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)

*Antibiotics given during hospitalization of enterococcal infection that has *in-vitro* activity against enterococci; $^{\Delta}$evaluated in vancomycin-susceptible enterococci; BMT = bone marrow transplant; ICU = intensive care unit; DAP = daptomycin; IV = intravenous

first day of 48 hours of negative cultures), 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). 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

Microbiologic data were obtained from available culture data during hospitalization, except for patients with osteomyelitis where culture data may include those from outpatient clinic visits, if available. Microbiologic 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 were performed by broth microdilution (BMD) and by Etest according to Clinical Laboratory Standards Institute guidelines and manufacturer instructions (bioMerieux, Durham, NC)(28), respectively. If the isolate was not available, the susceptibility interpretation and methodology were recorded from the referring institution.

Table 2
Baseline vancomycin and daptomycin minimum inhibitory concentration.

			DAP MIC (mg/L)								
			0.25	0.38	0.5	1	1.5	2	3	4	8
Enterococcus faecium											
VAN (mg/L)	MIC	≤4	--	--	--	1	1	--	--	1	--
		16-Aug	--	--	--				1	2	--
		≥32	--	--	--	8	6	38	11	53	1
Enterococcus faecalis											
VAN (mg/L)	MIC	≤4	--	--	1	2	--	1	--	--	--
		16-Aug	--	--	--	--	--	--	--	--	--
		≥32	1	1	1	3	4	4	--	2	--
Enterococcus spp.											
VAN (mg/L)	MIC	≤4	--	--	1	--	--	--	--	--	--
		16-Aug	--	--	--	--	--	--	--	1	--
		≥32	1	--	--	1	2	1	2	3	--
Total n = 155			2	1	3	15	13	44	14	62	1

VAN = vancomycin, DAP = daptomycin, MIC = minimum inhibitory concentration

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 ≥ 1000 IU/L (~ 5X ULN) or asymptomatic patients with CPK ≥ 2000 IU/L (≥ 10X 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; 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 vs. BMD and Etest) were analyzed for relationship by using Spearman's rank correlation. Clinical outcome was compared by Pearson's chi-square in relation to daptomycin MIC groups (≤ 2 mg/L versus > 2 mg/L).

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 2-6.5). The median dose and hospital duration of high-dose daptomycin was 8.2 mg/kg (IQR 7.7-9.7) and 10 days (IQR 6-15), respectively. One hundred and sixty-eight (68.6%) patients had doses of ≥ 8 mg/kg, 34 of these (13.9%) patients dosed ≥ 10 mg/kg. Two hundred fourteen (87.3%) patients received daptomycin interval of every 24 hours. Within our whole cohort, 43.7% (107/245) 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 organism 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. Minimum inhibitory concentration (MIC) of vancomycin is displayed in Table 2. One hundred fifty-five (63.3%) isolates had daptomycin susceptibility available from the medical charts. The MIC that inhibited growth of 50% (MIC_{50}) and 90% (MIC_{90}) of baseline enterococci isolates for daptomycin were 2 mg/L and 4 mg/L, respectively (see Table 2 for the frequency and distribution of institutional daptomycin MICs). Seventy-five enterococcal strains were recovered

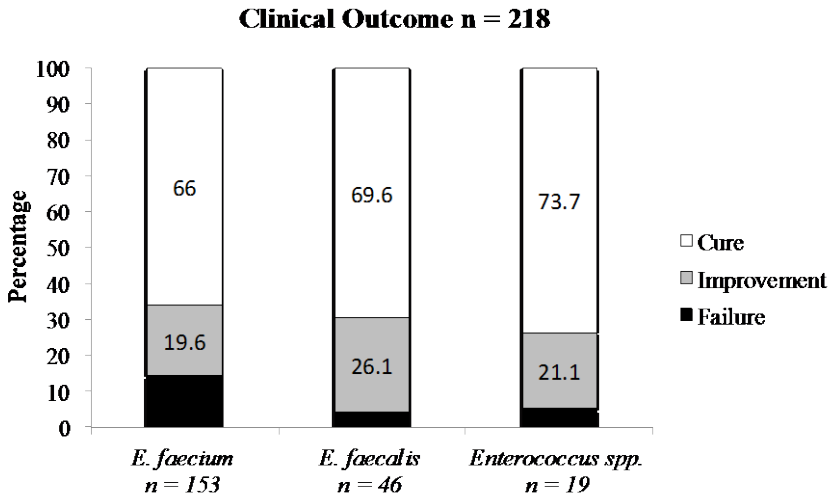

Figure 1. Clinical outcome proportion per enterococci species.
Frequency of clinical success for *E. faecium*, *E. faecalis*, and *Enterococcus* spp. were 85.6%, 95.7%, and 94.7%, respectively.

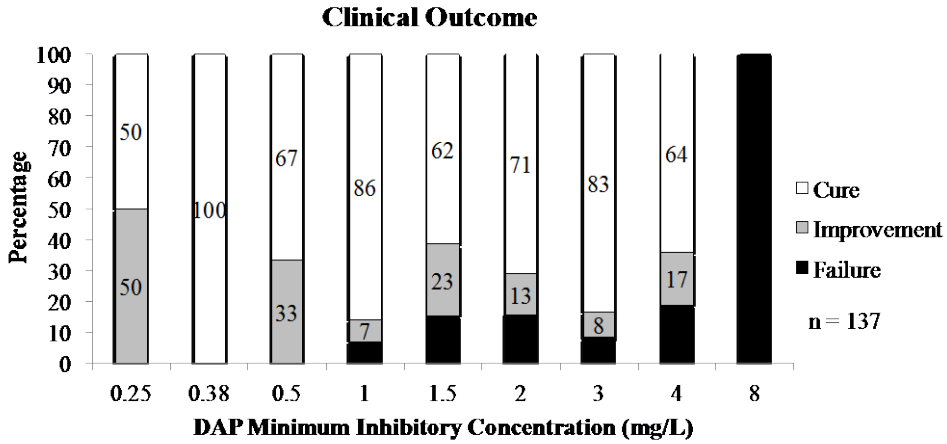

Figure 2. Clinical success stratified by daptomycin minimum inhibitory concentration.
DAP = daptomycin; Frequency of clinical success for daptomycin minimum inhibitory concentration for 0.25, 0.38, 0.5, 1.0, 1.5, 2, 3, 4, 8 mg/L were 100%, 100%, 100%, 93%, 85%, 84%, 91%, 81% and 0%, respectively.

for extended microbiologic 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 confirmed by both BMD and Etest. The MIC_{50} and MIC_{90} for these 75 enterococci isolates for daptomycin by both BMD and Etest were 1 mg/L and 2 mg/L, respectively. The median daptomycin MIC for *E. faecium* by BMD and Etest were 2 mg/L (range of 0.25-4 mg/L) and 2 mg/L (range of 0.5-4 mg/L), respectively. *E. faecalis* median daptomycin MIC by BMD and Etest were 0.5 mg/L (range 0.125-2 mg/L) and 1 mg/L (range 0.25-3 mg/L), respectively. The median daptomycin MIC for *Enterococcus* spp. by BMD and Etest were 1 mg/L (range 0.5-2 mg/L) and 1.5 mg/L (range 0.5-3 mg/L), respectively. Thirty-one enterococci 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 coefficient of 0.53 ($p = 0.002$) and 0.42 ($p = 0.019$), respectively.

Two hundred and eighteen (89%) patients were clinically evaluable; with 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. Proportion of clinical success by enterococci species is described in Figure 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 Figure 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 MIC $\leq$ 2 mg/L and MIC > 2 mg/L group respectively ($p = 0.371$). One hundred and 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 available patients, 32/33 (97%)

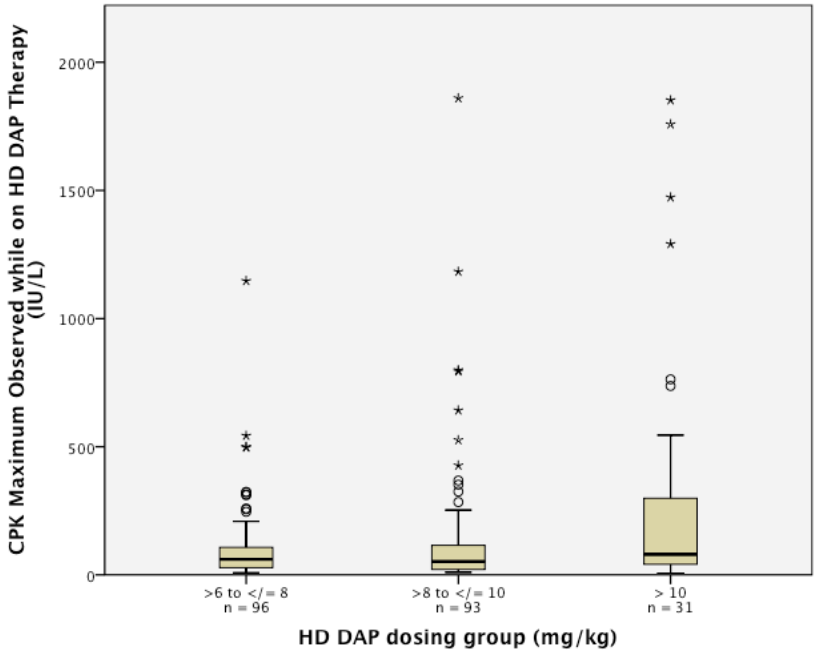

Figure 3. Maximum observed creatine phosphokinase level.
CPK = creatine phosphokinase; HD DAP = high dose daptomycin

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 2-5). Of the 14 patients with microbiologic persistence, 10 (71.4%) were complicated bacteremia, sites of infection included: 1 (7.1%) osteomyelitis, 2 (14.7%) skin and wound infection, 5 (35.7%) intra-abdominal infection, 4 (28.6%) IV catheter related infection, 1 (7.1%) left ventricular assist device and 1 (7.1%) right-sided infective endocarditis. Median duration of fever and leukocytosis during the enterococcal infection was 3 days (IQR 1-6) and 7 days (IQR 2-14.3), respectively. Median ICU length of stay and total length of stay was 8 days (IQR 3-15) and 22 days (IQR 13-39), respectively. Among the patients admitted to the ICU 85/125 (68%) were mechanically ventilated with median duration of mechanical ventilation was 8 days (IQR 2-14). All-cause in-hospital mortality was 19.6% (48/245) of patients. Of these 48 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%) were microbiologically eradicated. 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-3methylglutaryl-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 ≥ ULN that increased to 5x ULN while on high-dose daptomycin and the remaining six patients had a baseline CPK ≤ ULN that increased to 3x 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 characterized in Figure 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 ≥ 10x ULN saw a decrease in CPK to a level of 753 IU/L after 6 days of high-dose daptomycin (10.4 mg/kg every 24 hours) and remained asymptomatic throughout therapy. There was no reported myopathy or myositis while on high-dose daptomycin. All patients with CPK levels ≥ 5x ULN were asymptomatic and no patients were reported to have a CPK level increase to ≥ 10x ULN while on daptomycin. High-dose daptomycin was observed in one patient case to be safe up to 15.7 mg/kg (every 24 hours) for up to 14 days when used to treat VRE *faecium* complicated bacteremia from an abdominal source; the highest CPK level observed was 383 IU/L. The highest observed patient weight was 164 kg, who received daptomycin 8.2 mg/kg (every 24 hours) for 12 days and with no observation of CPK elevation for the treatment of VRE *faecium* infective endocarditis with the highest CPK level observed at 26 IU/L.

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 VRE *faecium* initial daptomycin MIC of 8

Table 3
Patients with VRE *faecitum* infections that developed nonsusceptibility to daptomycin.

Infection	Dose of HD-DAP (mg/kg)	Baseline DAP MIC (mg/L)	Days to MIC change while on HD-DAP	Subsequent DAP MIC (mg/L)	Outcome
Complicated IV catheter related BSI	8.2	2*	16	> 4*	Added gentamicin but expired during hospitalization
Complicated IV catheter related BSI	8.2	4*	13	> 4*	Discharged with HD-DAP with gentamicin DNS identified after D/C N/A for 30 days F/U
Complicated Prosthetic Device related BSI	6.17	1*	8	> 4*	Switched to LIN and cleared BSI N/A for 30 days F/U
Complicated BSI from skin/wound	10.1	4#	58	32#	Switched to Quinupristin/ Dalfopristin and cleared BSI Alive at 30 days F/U
Intra-abdominal	7.5	2#	13	24#	Switched to LIN and not other follow-up cultures Alive at 30 days F/U

HD-DAP = high-dose daptomycin; DAP = daptomycin; MIC = minimum inhibitory concentration; IV = intravenous; BSI = bloodstream infection; DNS = daptomycin nonsusceptibility; D/C = discharged from hospital; LIN = linezolid; N/A = not available; * = MIC identified by automated testing method from institution; # = MIC identified by Etest testing methodology

mg/L treated with vancomycin for three days and switched to high-dose daptomycin (7.94 mg/kg every 24 hours) for right-sided infective endocarditis once VRE was identified. Daptomycin was later switched to linezolid after seven days of high-dose daptomycin therapy and blood cultures cleared after three days of linezolid therapy (linezolid MIC of 2 mg/L). Five (2%) patients developed nonsusceptibility to daptomycin, with all isolates being VRE. *faecium*. These five patients were treated with high-dose daptomycin and description of infection, daptomycin dosages, MIC data, and outcome is 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 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 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 compared to 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 compared to the Cubicin® Outcomes Registry and Experience (CORE) study (53.2% vs. 27%) for treatment of enterococcal bacteremia(22). Our data had similar clinical success frequencies compared to the CORE data(22); in contrast, a higher frequency of microbiological cure (92.7%, 152/164) was observed compared to previous literature(21, 24). This improved outcome suggests 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 were higher compared to the CORE data, 8.2 mg/kg (range 6.02-15.70 mg/kg) and 6 mg/kg (range 2.9-14.8 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% vs. 46.3%, $p = 0.10$(32). The mortality was higher in the daptomycin group by Crank and colleagues but there were significant differences between the two treatments groups in baseline characteristics with a higher proportion of the daptomycin group having shock and have received previous treatment. Our enterococcal BSI hospital mortality was 23.7% (41/173), lower compared to Crank and colleagues retrospective cohort study. 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 Mave and colleagues' retrospective study (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 fre-

quency of microbiological cure was much higher in our study compared to 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 recent publication(36). This may be of interest, from a 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 vs. 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 appears 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 reported that high-dose daptomycin may elevate CPK level at an incidence of 2.5-8.3%(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, 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 is a multicenter observational investigation that incorporates a diverse cohort of adult patients across the United States; however this retrospective design does have some limitations. 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 is warranted.

ACKNOWLEDGEMENTS

This was an investigator-initiated study funded by Cubist Pharmaceuticals. The authors would like to acknowledge John Paul McRoberts (Anti-Infective Research Laboratory, Wayne State University) for assistance in the extended microbiological assessment and verification.

REFERENCES

1. **Biedenbach, D. J., G. J. Moet, and R. N. Jones.** 2004. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagn Microbiol Infect Dis **50:**59-69.
2. **Carmeli, Y., G. Eliopoulos, E. Mozaffari, and M. Samore.** 2002. Health and economic outcomes of vancomycin-resistant enterococci. Arch Intern Med **162:**2223-2228.
3. **Bhavnani, S. M., J. A. Drake, A. Forrest, J. A. Deinhart, R. N. Jones, D. J. Biedenbach, and C. H. Ballow.** 2000. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. Diagn Microbiol Infect Dis **36:**145-158.
4. **Hidron, A. I., J. R. Edwards, J. Patel, T. C. Horan, D. M. Sievert, D. A. Pollock, and S. K. Fridkin.** 2008. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol **29:**996-1011.
5. **Wisplinghoff, H., T. Bischoff, S. M. Tallent, H. Seifert, R. P. Wenzel, and M. B. Edmond.** 2004. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **39:**309-317.
6. Linezolid (Zyvox) Package Insert. Pharmacia & Upjohn Co. Division of Pfizer Inc., March 2012, New York, New York.
7. **Chong, Y. P., S. O. Lee, E. H. Song, E. J. Lee, E. Y. Jang, S. H. Kim, S. H. Choi, M. N. Kim, J. Y. Jeong, J. H. Woo,**

and Y. S. Kim. 2010. Quinupristin-dalfopristin versus linezolid for the treatment of vancomycin-resistant Enterococcus faecium bacteraemia: efficacy and development of resistance. Scand J Infect Dis **42:**491-499.
8. **Raad, I., R. Hachem, H. Hanna, C. Afif, C. Escalante, H. Kantarjian, and K. Rolston.** 2004. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant Enterococcus faecium infections. J Antimicrob Chemother **53:**646-649.
9. **Pogue, J. M., D. L. Paterson, A. W. Pasculle, and B. A. Potoski.** 2007. Determination of risk factors associated with isolation of linezolid-resistant strains of vancomycin-resistant Enterococcus. Infection control and hospital epidemiology **28:**1382-1388.
10. **Hachem, R. Y., K. Hicks, A. Huen, and I. Raad.** 2003. Myelosuppression and serotonin syndrome associated with concurrent use of linezolid and selective serotonin reuptake inhibitors in bone marrow transplant recipients. Clin Infect Dis **37:**e8-11.
11. **Baddour, L. M., W. R. Wilson, A. S. Bayer, V. G. Fowler, Jr., A. F. Bolger, M. E. Levison, P. Ferrieri, M. A. Gerber, L. Y. Tani, M. H. Gewitz, D. C. Tong, J. M. Steckelberg, R. S. Baltimore, S. T. Shulman, J. C. Burns, D. A. Falace, J. W. Newburger, T. J. Pallasch, M. Takahashi, and K. A. Taubert.** 2005. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation **111:**e394-434.
12. **Arbeit, R. D., D. Maki, F. P. Tally, E. Campanaro, and B. I. Eisenstein.** 2004. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis **38:**1673-1681.
13. **Fowler, V. G., Jr., H. W. Boucher, G. R. Corey, E. Abrutyn, A. W. Karchmer, M. E. Rupp, D. P. Levine, H. F. Chambers, F. P. Tally, G. A. Vigliani, C. H. Cabell, A. S. Link, I. DeMeyer, S. G. Filler, M. Zervos, P. Cook, J. Parsonnet, J. M. Bernstein, C. S. Price, G. N. Forrest, G. Fatkenheuer, M. Gareca, S. J. Rehm, H. R. Brodt, A. Tice, and S. E. Cosgrove.** 2006. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med **355:**653-665.
14. **Rose, W. E., M. J. Rybak, and G. W. Kaatz.** 2007. Evaluation of daptomycin treatment of Staphylococcus aureus bacterial endocarditis: an in vitro and in vivo simulation using historical and current dosing strategies. J Antimicrob Chemother **60:**334-340.
15. Daptomycin (Cubicin) Package Insert. Cubist Pharmaceuticals, Inc., Lexington, Massachusetts.
16. **Akins, R. L., and M. J. Rybak.** 2001. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus faecium, and methicillin-resistant Staphylococcus aureus isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations. Antimicrob Agents Chemother **45:**454-459.
17. **Segreti, J. A., C. W. Crank, and M. S. Finney.** 2006. Daptomycin for the treatment of gram-positive bacteremia and infective endocarditis: a retrospective case series of 31 patients. Pharmacotherapy **26:**347-352.
18. **Levine, D. P., and K. C. Lamp.** 2007. Daptomycin in the treatment of patients with infective endocarditis: experience from a registry. Am J Med **120:**S28-33.
19. **Kelesidis, T., R. Humphries, D. Z. Uslan, and D. A. Pegues.** 2011. Daptomycin nonsusceptible enterococci: an emerging challenge for clinicians. Clin Infect Dis **52:**228-234.
20. **Moise, P. A., E. Hershberger, M. I. Amodio-Groton, and K. C. Lamp.** 2009. Safety and clinical outcomes when utilizing high-dose (> or =8 mg/kg) daptomycin therapy. Ann Pharmacother **43:**1211-1219.
21. **Kullar, R., S. L. Davis, D. P. Levine, J. J. Zhao, C. W. Crank, J. Segreti, G. Sakoulas, S. E. Cosgrove, and M. J. Rybak.** 2011. High-dose daptomycin for treatment of complicated gram-positive infections: a large, multicenter, retrospective study. Pharmacotherapy **31:**527-536.
22. **Mohr, J. F., L. V. Friedrich, S. Yankelev, and K. C. Lamp.** 2009. Daptomycin for the treatment of enterococcal bacteraemia: results from the Cubicin Outcomes Registry and Experience (CORE). Int J Antimicrob Agents **33:**543-548.
23. **King, E. A., D. McCoy, S. Desai, T. Nyirenda, and K. Bicking.** 2011. Vancomycin-resistant enterococcal bacteraemia and daptomycin: are higher doses necessary? J Antimicrob Chemother **66:**2112-2118.
24. **Gallagher, J. C., M. E. Perez, E. A. Marino, L. G. LoCastro, L. A. Abrardo, and C. MacDougall.** 2009. Daptomycin therapy for vancomycin-resistant enterococcal bacteremia: a retrospective case series of 30 patients. Pharmacotherapy **29:**792-799.
25. **Lodise, T. P., P. S. McKinnon, V. H. Tam, and M. J. Rybak.** 2002. Clinical outcomes for patients with bacteremia caused by vancomycin-resistant enterococcus in a level 1 trauma center. Clin Infect Dis **34:**922-929.
26. **Li, J. S., D. J. Sexton, N. Mick, R. Nettles, V. G. Fowler, Jr., T. Ryan, T. Bashore, and G. R. Corey.** 2000. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **30:**633-638.
27. **Lew, D. P., and F. A. Waldvogel.** 2004. Osteomyelitis. Lancet **364:**369-379.
28. 2010. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing, Sixteenth Informational Supplement. CLSI Document M100-S20 ed. CLSI, Wayne, PA.
29. **Bhavnani, S. M., C. M. Rubino, P. G. Ambrose, and G. L. Drusano.** 2010. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis **50:**1568-1574.
30. **Shay, D. K., S. A. Maloney, M. Montecalvo, S. Banerjee, G. P. Wormser, M. J. Arduino, L. A. Bland, and W. R. Jarvis.** 1995. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. J Infect Dis **172:**993-1000.
31. **Lucas, G. M., N. Lechtzin, D. W. Puryear, L. L. Yau, C. W. Flexner, and R. D. Moore.** 1998. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: comparison of clinical features and outcomes. Clin Infect Dis **26:**1127-1133.
32. **Crank, C. W., M. H. Scheetz, B. Brielmaier, W. E. Rose, G. P. Patel, D. J. Ritchie, and J. Segreti.** 2010. Comparison of outcomes from daptomycin or linezolid treatment for vancomycin-resistant enterococcal bloodstream infection: A

retrospective, multicenter, cohort study. Clin Ther **32:**1713-1719.

33. **Mave, V., J. Garcia-Diaz, T. Islam, and R. Hasbun.** 2009. Vancomycin-resistant enterococcal bacteraemia: is daptomycin as effective as linezolid? J Antimicrob Chemother **64:**175-180.
34. **Rand, K. H., and H. Houck.** 2004. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. J Antimicrob Chemother **53:**530-532.
35. **Sakoulas, G., A. S. Bayer, J. Pogliano, B. T. Tsuji, S. J. Yang, N. N. Mishra, V. Nizet, M. R. Yeaman, and P. A. Moise.** 2012. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant Enterococcus faecium. Antimicrob Agents Chemother **56:**838-844.
36. **Moise, P. A., K. C. Lamp, D. D. DePestel, M. J. Yoon, and M. J. Zervos.** September 9-12, 2012. Daptomycin (D) with or without Concomitant Beta-lactams (BL) for Vancomycin-Resistant Enterococcus (VRE) Bacteremia, Presented as poster at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA.
37. **De Rosa, F. G., O. Mollaretti, C. Cometto, N. Pagani, C. Montrucchio, and G. Di Perri.** 2009. Early experience with high-dosage daptomycin for prosthetic infections. Clin Infect Dis **49:**1772-1773.
38. **Katz, D. E., K. C. Lindfield, J. N. Steenbergen, D. P. Benziger, K. J. Blackerby, A. G. Knapp, and W. J. Martone.** 2008. A pilot study of high-dose short duration daptomycin for the treatment of patients with complicated skin and skin structure infections caused by gram-positive bacteria. Int J Clin Pract **62:**1455-1464.
39. **Figueroa, D. A., E. Mangini, M. Amodio-Groton, B. Vardianos, A. Melchert, C. Fana, W. Wehbeh, C. M. Urban, and S. Segal-Maurer.** 2009. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis **49:**177-180.
40. **Durante-Mangoni, E., R. Casillo, M. Bernardo, C. Caianiello, I. Mattucci, D. Pinto, F. Agrusta, R. Caprioli, R. Albisinni, E. Ragone, and R. Utili.** 2012. High-dose daptomycin for cardiac implantable electronic device-related infective endocarditis. Clin Infect Dis **54:**347-354.
41. **Rege, S., J. Mohr, K. C. Lamp, M. Yoon, and K. C. Lindfield.** 2013. Safety of daptomycin in patients completing more than 14 days of therapy: results from the Cubicin((R)) Outcomes Registry and Experience. Int J Antimicrob Agents.