Impact of Different Antimicrobial Therapies on Clinical and Fiscal Outcomes of Patients with Bacteremia Due to Vancomycin-Resistant Enterococci

Kayoko Hayakawa,^{a,b} Emily T. Martin,^c Uma Mahesh Gudur,^a Dror Marchaim,^a Dalia Dalle,^a Khaled Alshabani,^a Kalyan Srinivas Muppavarapu,^a Fnu Jaydev,^a Pradeep Bathina,^a Pranathi Rao Sundaragiri,^a Shashi Dhar Rajuri,^a Jaikumar Khatri,^a Jason M. Pogue,^{a,d} Paul R. Lephart,^e Michael J. Rybak,^{a,f} Keith S. Kaye^a

Division of Infectious Diseases, Wayne State University, Detroit Medical Center, Detroit, Michigan, USA^a; Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan^b; Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA^c; Department of Pharmacy Services, Detroit Medical Center, Detroit, Michigan, USA^d; Detroit Medical Center University Laboratories, Detroit, Michigan, USA^e; Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA^f

Vancomycin-resistant enterococci (VRE) are a growing health problem, and uncertainties exist regarding the optimal therapy for bloodstream infection due to VRE. We conducted systematic comparative evaluations of the impact of different antimicrobial therapies on the outcomes of patients with bloodstream infections due to VRE. A retrospective study from January 2008 to October 2010 was conducted at Detroit Medical Center. Unique patients with blood cultures due to VRE were included and reviewed. Three major therapeutic classes were analyzed: daptomycin, linezolid, and β -lactams. Three multivariate models were conducted for each outcome, matching for a propensity score predicting the likelihood of receipt of one of the therapeutic classes. A total of 225 cases of bacteremia due to VRE were included, including 86 (38.2%) cases of VR *Enterococcus faecalis* and 139 (61.8%) of VR *Enterococcus faecium*. Bacteremia due to VR *E. faecalis* was more frequent among subjects treated with β -lactams than among those treated with daptomycin or linezolid. The median dose of daptomycin was 6 mg/kg of body weight (range, 6 to 12 mg/kg). After controlling for propensity score and bacteremia due to VR *E. faecalis*, differences in mortality were nonsignificant among the treatment groups. Therapy with daptomycin was associated with higher median variable direct cost per day than that for linezolid. This large study revealed the three therapeutic classes (daptomycin, linezolid, and β -lactams) are similarly efficacious in the treatment of bacteremia due to susceptible strains of VRE.

Vancomycin-resistant enterococci (VRE) are major clinical and epidemiological threats; vancomycin resistance in the United States occurs in approximately 80% to 95% in *Enterococcus faecium* and 5 to 7% in *Enterococcus faecalis* (1, 2). At the Detroit Medical Center (DMC), 12.5% of 4,377 ($n = 547$) isolates of *E. faecalis* and 75.2% of 1,150 ($n = 865$) isolates of *E. faecium* in 2009 were VRE (3).

Treatment options are limited for bacteremia due to VRE. The preferred treatment for VRE bacteremia is ampicillin if the isolate is susceptible to this agent. However, the majority of VR *E. faecium* isolates are resistant to ampicillin (2, 4). Newer agents, such as linezolid or daptomycin, are additional treatment options. Linezolid, which was approved by the FDA for the treatment of VRE infections, may be given parenterally or orally (4). However, linezolid is bacteriostatic *in vivo* against enterococci (4). Despite its bactericidal activity against most Gram-positive organisms, including VRE, daptomycin is not FDA approved for the treatment of VRE infections. Other available agents with antienterococcal activity have major limitations (4).

Uncertainties exist regarding the optimal treatment for bloodstream infection due to VRE, particularly when ampicillin cannot be used. Because VRE is a growing health problem, it is imperative to obtain further information on optimal treatment for bacteremia due to VRE. We conducted systematic comparative evaluations of the impact of different antimicrobial therapies on the outcomes of patients with bloodstream infections due to VRE.

MATERIALS AND METHODS

Study settings and design. A retrospective analysis to evaluate the impact of different antimicrobial therapies on clinical and fiscal outcomes of patients with bacteremia due to VRE was conducted at DMC, which consists of 8 hospitals. Institutional review boards at Wayne State University and DMC approved the study before its initiation.

Patients and variables. The study cohort consisted of all patients who had a positive blood culture for VR *E. faecalis* or VR *E. faecium* as identified by the DMC clinical microbiology laboratory from 1 January 2008 to 31 October 2010. For patients who had >1 episode of bacteremia due to VRE during the study period, only the first episode of VRE bacteremia was analyzed. Patients who did not receive effective intravenous therapy for >24 h were excluded. Oral as well as intravenous linezolid therapy was considered to be effective. Patients who received daptomycin at a dose of <6 mg/kg were excluded from the study. Effective therapy was defined based on *in vitro* activity as reported by the DMC clinical microbiology

Received 7 April 2014 Returned for modification 15 April 2014

Accepted 22 April 2014

Published ahead of print 5 May 2014

Address correspondence to Kayoko Hayakawa, kayokohayakawa@gmail.com.

Supplemental material for this article may be found at <http://dx.doi.org/10.1128/AAC.02943-14>.

Copyright © 2014, American Society for Microbiology. All Rights Reserved.

doi:10.1128/AAC.02943-14

laboratory, in accordance with the Clinical and Laboratory Standard Institutions (CLSI) criteria (5).

Parameters retrieved from patient records included (i) demographics, (ii) comorbid conditions (including components of Charlson's scores [6]) and immunosuppressive status, (iii) recent health care-associated exposures, (iv) acute illness indices, including McCabe score (7), and the severity of sepsis levels per systemic inflammatory response syndrome (SIRS) criteria (8), (v) infectious clinical syndromes causing bacteremia, (vi) whether the VRE bacteremia was community or hospital onset, (vii) factors related to antimicrobial therapy, and (viii) outcomes. Immunosuppressive status included one or more of the following: neutropenia (<500 neutrophils) at time of culture, glucocorticoid/steroid use in the past month, chemotherapy or radiotherapy in the past 3 months, HIV, being a transplant recipient, or anti-tumor necrosis factor alpha (TNF- α) therapy in the past 3 months. Infectious clinical syndromes causing bacteremia were determined based on CDC/NHSN definitions and IDSA guidelines (9–11), infectious disease consultation notes, primary care team progress notes, and SIRS criteria (8). For cases categorized as catheter-related bloodstream infection (CRBSI), information pertaining to catheter removal was obtained. Hospital-acquired VRE was defined as length of hospital stay (LOS) before VRE isolation of >2 days. Factors related to antimicrobial therapy included recent (within 3 months) exposures to antimicrobials, empirical therapy (defined as therapy administered from 48 h before to 72 h following VRE culture date), and the main "consolidative" regimen (i.e., antibiotics provided from 72 h to 14 days following VRE isolation). Time to effective therapy (the number of hours from the time of VRE isolation from the blood to the time of initiation of effective therapy) and hours of effective therapy (the duration of effective antimicrobial therapy administered from 48 h before to 2 weeks following the VRE culture date) were also analyzed. Information regarding switching and combinations of antibiotic therapies from 72 h to 14 days following VRE isolation were also obtained, and switching agents due to treatment failure was defined by the presence of sustained bacteremia when the therapeutic agent was switched. Outcomes included in-hospital and 90-day mortality, LOS, functional status deterioration (deterioration from the time of admission to discharge in ≥ 1 activities of daily living according to Katz criteria [12]), and discharge to a long-term facility after being admitted from home. Mortality refers to all-cause mortality throughout this report. Direct hospital costs were obtained from administrative financial databases.

Microbiology. DMC has a single centralized Clinical Microbiology Laboratory. Bacteria are identified to the species level, and susceptibilities are determined to predefined antimicrobials, based on an automated broth microdilution system (MicroScan; Siemens AG, Germany), and in accordance with the CLSI criteria (5). All results of MicroScan are assessed by a medical technologist in the microbiology laboratory, and supplemental tests are utilized when indicated (e.g., atypical susceptibility patterns of enterococci). At DMC, $>99\%$ concordance of susceptibility between ampicillin and penicillin has been observed, and, thus, we considered ampicillin-sensitive isolates to be piperacillin sensitive (13).

Surveillance cultures for VRE were not conducted routinely at DMC during the study period and were excluded from the analysis.

Statistical analysis. All analyses were performed by using SPSS 20 (Chicago, IL; 2012) and SAS software, version 9.3 (SAS Institute). As we were unable to obtain direct hospital costs on patients who were admitted to a cancer institute that is physically part of DMC, two separate cohorts for analyses were used; the entire cohort, used for analyses on mortality and LOS; and the cohort with hospital cost data for analysis of fiscal outcomes, which excluded cancer institute patients. Bivariate analyses performed included Fisher's exact test and chi-square test for categorical variables and independent sample *t* test or the Mann-Whitney *U* test for continuous variables. Three multivariate propensity models were constructed predicting the likelihood of receipt of one of the therapeutic classes (i.e., daptomycin versus linezolid, daptomycin versus β -lactams, linezolid versus β -lactams). Propensity scores predicting the likelihood of

receipt of one of the therapeutic classes were developed for each subject based on the β -coefficients of variables in multivariate models. Separate propensity scores were calculated for the whole cohort and the cost data cohort, which excluded cancer center patients. For each comparison, cases from each treatment group were matched based on propensity score in a 1:1 ratio using a range of ± 0.5 propensity score points. Cases for which there was no available match were excluded. To evaluate the impact of different antimicrobial therapies on clinical and fiscal outcomes of patients with bacteremia due to VRE, multivariable regression models were constructed for in-hospital mortality (logistic regression) and for LOS after VRE bacteremia (excluding those who died) and increased cost (linear regression on natural log-transformed LOS and cost).

The effect estimates for LOS and cost were reported as the multiplicative effect (the antilog of the β -coefficient) (14).

For all analyses, a *P* value of 0.05 was considered significant. All variables with a *P* value of <0.1 in the bivariate analyses, and which were not included in the propensity score model, were considered for inclusion in the multivariate outcome analyses. A stepwise selection procedure was used to select variables for inclusion in the final model. The final model was tested for confounding variables to assess any additional impact on the model. If a covariate affected the β -coefficient of a variable in the model by $>10\%$, then the confounding variable was maintained in the multivariable model. All *P* values were two-sided.

RESULTS

Entire cohort. During the study period, 225 cases of VRE bacteremia met inclusion criteria. Eighty-six (38%) cases of bacteremia were due to VR *E. faecalis*, and 139 (62%) were due to VR *E. faecium*. Fifty-six cases were treated with daptomycin, 112 cases were treated with linezolid, and 57 cases were treated with β -lactams. The median dose of daptomycin was 6 mg/kg (range, 6 to 12 mg/kg). Among the patients treated with β -lactams, 42 (74%) received ampicillin, 9 (16%) received piperacillin-tazobactam, and 6 (11%) received ampicillin-sulbactam.

Bivariate analyses comparing characteristics of patients within each treatment group are displayed in Table 1. Bacteremia due to VR *E. faecalis* was more frequent among the β -lactam group than the daptomycin/linezolid group. Patients in the daptomycin group were more frequently immunosuppressed or had hematologic malignancy compared to patients in the β -lactam/linezolid group. Concurrent bloodstream infections (within 3 days of VRE culture) due to organisms other than VRE were more common among patients in the β -lactam group than in the daptomycin and linezolid groups. The most common pathogen isolated among patients with concurrent bloodstream infection was coagulase-negative staphylococci ($n = 46$), followed by Gram-negative bacilli ($n = 34$), *Staphylococcus aureus* ($n = 11$), and *Candida* spp. ($n = 5$).

The most common source of bacteremia in each group was a central venous catheter (i.e., CRBSI cases [$n = 89, 40\%$]). Among patients with CRBSI, the central line was removed in 14 patients (68%) within the daptomycin group, 34 (72%) within the linezolid group, and 18 (81%) within the β -lactam group. The proportion of patients who had their catheter removed did not differ among each treatment group ($P > 0.05$ for each 2-group comparison).

A urinary source of infection was more common in the β -lactam than the daptomycin group, and the proportion of subjects with an unknown primary source of bacteremia was more common in the daptomycin group than the linezolid/ β -lactam group.

The frequency of combination therapy did not significantly differ among groups. The most commonly used agent in combi-

TABLE 1 Bivariate analysis of bacteremia due to VRE as a function of type of antimicrobial therapy^a

Parameter	Value			OR			P value		
	DAP (n = 56)	LZD (n = 112)	BL (n = 57)	DAP vs LZD	DAP vs BL	LZD vs BL	DAP vs LZD	DAP vs BL	LZD vs BL
Demographics									
Mean age in yrs (±SD)	54.6 (±14.6)	63.8 (±15.1)	64.1 (±14.5)				<0.01	<0.01	0.91
Age ≥65 yrs	15 (26.8)	51 (45.5)	29 (50.9)	0.4 (0.2–0.9)	0.4 (0.2–0.8)	0.8 (0.4–1.5)	0.02	0.01	0.52
Male gender	33 (58.9)	60 (53.6)	33 (57.9)	0.8 (0.4–1.5)	1.0 (0.5–2.0)	1.2 (0.6–2.3)	0.62	>0.99	0.63
African-American	29 (51.8)	79 (70.5)	50 (87.7)	0.5 (0.2–0.9)	0.3 (0.1–0.4)	0.3 (0.1–0.8)	0.03	<0.01	0.01
Non-home residence	19 (33.9)	51 (45.5)	28 (49.1)	0.6 (0.3–1.2)	0.5 (0.3–1.1)	0.9 (0.5–1.6)	0.19	0.13	0.75
Acute and chronic conditions on admission									
Dependent functional status	41 (73.2)	76 (67.9)	42 (73.7)	1.3 (0.6–2.6)	1.0 (0.4–2.3)	0.8 (0.4–1.5)	0.59	>0.99	0.48
Rapidly fatal McCabe score	13 (23.2)	27 (24.3)	16 (28.1)	0.9 (0.4–2.0)	0.8 (0.3–1.8)	0.8 (0.4–1.7)	>0.99	0.67	0.71
Diabetes mellitus	17 (30.4)	60 (53.6)	32 (56.1)	0.4 (0.2–0.8)	0.3 (0.2–0.7)	0.9 (0.5–1.7)	0.01	0.01	0.87
Dementia	5 (8.9)	24 (21.4)	11 (19.3)	0.3 (0.1–1.0)	0.4 (0.1–1.3)	1.1 (0.5–2.5)	0.05	0.18	0.84
Neurologic diseases	15 (26.8)	27 (24.1)	30 (52.6)	1.2 (0.6–2.4)	0.3 (0.2–0.7)	0.3 (0.2–0.6)	0.71	0.01	<0.01
Median Charlson's weighted index	4 (2–7)	4 (2–7)	5 (3–7)				0.26	0.03	0.32
comorbidity score (IQR)									
Immunosuppressive state ^b	27 (48.2)	31 (27.7)	12 (21.1)	2.4 (1.3–4.7)	3.5 (1.5–8.0)	1.4 (0.7–3.1)	0.01	<0.01	0.46
Hematologic malignancy	17 (30.4)	4 (3.6)	1 (1.8)	11.8 (3.7–37.1)	24.4 (3.1–191.1)	2.1 (0.2–19.0)	<0.01	<0.01	0.66
Chronic skin ulcers	11 (19.6)	36 (32.1)	28 (49.1)	0.5 (0.2–1.1)	0.3 (0.1–0.6)	0.5 (0.3–0.9)	0.10	<0.01	0.04
Exposure to health care settings and environments before VRE isolation									
Hospitalized in the past 3 mo	43 (76.8)	81 (72.3)	46 (80.7)	1.3 (0.6–2.7)	0.8 (0.3–2.0)	0.6 (0.3–1.4)	0.58	0.65	0.26
Chronic hemodialysis	11 (19.6)	32 (28.6)	24 (42.1)	0.6 (0.3–1.3)	0.3 (0.2–0.8)	0.6 (0.3–1.1)	0.26	0.01	0.09
Surgery or invasive procedure in the past 6 mo	49 (87.5)	84 (75.0)	38 (66.7)	2.3 (1.0–5.7)	3.5 (1.3–9.2)	1.5 (0.8–3.0)	0.07	0.01	0.28
Permanent devices ^c	41 (74.5)	97 (86.6)	49 (86)	0.5 (0.2–1.0)	0.5 (0.2–1.3)	1.1 (0.4–2.7)	0.080	0.16	>0.99
ICU stay at the time of VRE isolation	28 (50)	56 (50)	16 (28.1)	1.0 (0.5–1.9)	2.6 (1.2–5.6)	2.6 (1.3–5.1)	0.999	0.02	0.01
ICU stay in past 3 mo prior to VRE isolation	32 (57.1)	66 (58.9)	22 (38.6)	0.9 (0.5–1.8)	2.1 (1.0–4.5)	2.3 (1.2–4.4)	0.869	0.01	0.02
Microbiology									
Bacteremia due to VR <i>E. faecalis</i>	8 (14.3)	24 (21.4)	54 (94.7)	0.6 (0.3–1.5)	0.01 (0–0.04)	0.02 (0–0.05)	0.30	<0.01	<0.01
Hospital-acquired VRE ^d	43 (76.8)	62 (55.4)	18 (31.6)	2.7 (1.3–5.5)	7.2 (3.1–16.5)	2.7 (1.4–5.3)	0.01	<0.01	0.01
Median LOS prior to VRE isolation in days (IQR)	9 (1–23)	5 (1–18)	1 (0–5)				0.08	<0.001	<0.01
Concurrent bacteremia due to other organism within 3 days of VRE isolation	17 (30.4)	47 (42.0)	34 (59.6)	0.6 (0.3–1.2)	0.3 (0.1–0.6)	0.5 (0.3–0.9)	0.18	<0.01	0.04
Antimicrobial exposure within 3 mo prior to VRE isolation									
Any antibiotics	43 (76.8)	87 (77.7)	41 (71.9)	1.0 (0.4–2.0)	1.3 (0.6–3.0)	1.4 (0.7–2.8)	>0.99	0.67	0.45
Penicillins ^e	12 (21.4)	35 (31.2)	15 (26.3)	0.6 (0.3–1.3)	0.8 (0.3–1.8)	1.3 (0.6–2.6)	0.21	0.66	0.59
Cephalosporins	31 (55.4)	58 (51.8)	32 (56.1)	1.2 (0.6–2.2)	1.0 (0.5–2.0)	0.8 (0.4–1.6)	0.74	>0.99	0.63
Carbapenems	13 (23.2)	15 (13.4)	5 (8.8)	2.0 (0.9–4.5)	3.1 (1.0–9.5)	1.6 (0.6–4.7)	0.13	0.04	0.46
Fluoroquinolones	7 (12.5)	25 (22.3)	10 (17.5)	0.5 (0.2–1.2)	0.7 (0.2–1.9)	1.4 (0.6–3.1)	0.15	0.60	0.55
Vancomycin	27 (48.2)	54 (48.2)	31 (54.4)	1.0 (0.5–1.9)	0.8 (0.4–1.6)	0.8 (0.4–1.5)	>0.99	0.57	0.52
Aminoglycosides	7 (12.5)	8 (7.1)	6 (10.5)	1.9 (0.6–5.4)	1.2 (0.4–3.9)	0.7 (0.2–2.0)	0.26	0.78	0.56
Daptomycin	8 (14.3)	1 (0.9)	1 (1.8)	18.5 (2.3–152.0)	9.3 (1.1–77.3)	0.5 (0.0–8.2)	<0.01	0.02	>0.99
Linezolid	2 (3.6)	4 (3.6)	4 (7.0)	1.0 (0.2–5.6)	0.5 (0.1–2.8)	0.5 (0.1–2.0)	>0.99	0.68	0.45
Clindamycin	5 (8.9)	13 (11.6)	3 (5.3)	0.8 (0.3–2.2)	2.3 (0.7–7.1)	2.4 (0.7–8.7)	0.79	0.49	0.27
Metronidazole	10 (17.9)	15 (13.4)	5 (8.8)	1.4 (0.6–3.4)	1.8 (0.4–7.8)	1.6 (0.6–4.7)	0.49	0.18	0.46
Severity of illness indices at the time of VRE isolation									
Severe sepsis/septic shock/multiorgan failure per SIRS criteria (8)	10 (18.2)	16 (15)	9 (16.4)	1.3 (0.5–3.0)	1.1 (0.4–3.1)	0.9 (0.4–2.2)	0.65	>0.99	0.82
Transferred to ICU	14 (25)	27 (24.3)	15 (26.3)	1.0 (0.5–2.2)	0.9 (0.4–2.2)	0.9 (0.4–1.9)	>0.99	>0.99	0.85
Necessitated acute mechanical intubation/ventilation	16 (28.6)	29 (26.1)	12 (21.1)	1.1 (0.6–2.3)	1.5 (0.6–3.6)	1.3 (0.6–2.9)	0.85	0.39	0.57
Developed acute renal failure ^f	23 (41.1)	37 (33)	26 (45.6)	1.4 (0.7–2.7)	0.8 (0.4–1.8)	0.6 (0.3–1.1)	0.31	0.705	0.13
Developed acute liver injury ^g	9 (16.4)	8 (7.1)	2 (3.6)	2.5 (0.9–7.0)	5.2 (1.1–25.2)	2.0 (0.4–9.9)	0.10	0.052	0.50
Infectious clinical syndromes causing bacteremia									
Catheter-related bloodstream infection	20 (35.7)	47 (42)	22 (38.6)	0.8 (0.6–1.6)	0.9 (0.4–2.0)	1.2 (0.6–2.3)	0.44	0.75	0.67
Skin and soft tissue infection	12 (21.4)	24 (21.4)	12 (21.1)	1.0 (0.4–2.3)	1.0 (0.4–2.8)	1.0 (0.4–2.4)	>0.99	0.96	0.96
Intraabdominal infection	7 (12.5)	15 (13.4)	6 (10.5)	0.9 (0.3–2.6)	1.2 (0.3–4.5)	1.3 (0.4–4.1)	0.87	0.74	0.59
Urinary tract infection	2 (3.6)	13 (11.6)	9 (15.8)	0.3 (0.0–1.4)	0.2 (0.0–1.1)	0.7 (0.3–1.9)	0.15	0.06	0.60
Focus unknown	10 (17.9)	7 (6.2)	3 (5.3)	3.3 (1.1–10.2)	3.9 (0.9–19.2)	1.2 (0.3–6.1)	0.04	0.07	0.80
Contamination or catheter colonization	2 (3.6)	4 (3.6)	4 (7)	1.0 (0.1–6.6)	0.5 (0.1–3.3)	0.5 (0.1–2.5)	>0.99	0.41	0.32
Infective endocarditis	2 (3.6)	2 (1.8)	1 (1.8)	2.0 (0.2–20.9)	2.1 (0.1–59.6)	1.0 (0.1–29.0)	0.47	0.55	>0.99

(Continued on following page)

TABLE 1 (Continued)

Parameter	Value			OR			P value		
	DAP (<i>n</i> = 56)	LZD (<i>n</i> = 112)	BL (<i>n</i> = 57)	DAP vs LZD	DAP vs BL	LZD vs BL	DAP vs LZD	DAP vs BL	LZD vs BL
Antimicrobial therapy									
Time to effective therapy ^b in h (IQR)	36 (17–56)	64 (28–86)	43 (20–64)				<0.01	0.25	0.02
Duration of effective therapy in h (IQR)	109 (52–248)	166 (72–301)	200 (89–293)				0.11	0.03	0.36
Duration of effective therapy, excluding those who died, in h (IQR)	113 (53–334)	197 (82–336)	197 (101–282)				0.14	0.15	0.97
Combination therapy	6 (10.7)	8 (7.1)	9 (15.8)	1.6 (0.5–4.7)	0.6 (0.2–1.9)	0.4 (0.2–1.1)	0.56	0.58	0.10
Switching therapy	8 (16.7)	14 (14.3)	7 (14)	1.2 (0.4–3.2)	1.2 (0.4–4.0)	1.0 (0.4–3.0)	0.75	0.74	0.97
Switching therapy due to treatment failure ⁱ	0	3 (2.8)	2 (3.6)	0 (0–4.5)	0 (0–4.18)	0.8 (0.1–6.7)	0.22	0.16	0.76

^a These analyses were on unmatched cohorts. Boldface indicates statistically significant difference between groups ($P < 0.05$). BL, β -lactam; DAP, daptomycin; ICU, intensive care unit; IQR, interquartile range; LZD, linezolid; LOS, length of hospital stay; LTCF, long-term care facility; SIRS, systemic inflammatory response syndrome; OR, odds ratio. Values are no. (%) of patients unless otherwise indicated. The percentages are of patients for whom data were available, i.e., excluding the missing cases.

^b Includes one or more of the following: (i) neutropenia (<500 neutrophils) at time of culture; (ii) glucocorticoid/steroid use in the past month; (iii) chemotherapy in the past 3 months; (iv) radiotherapy in the past 3 months; (v) HIV; (vi) posttransplantation; or (vii) anti-TNF- α therapy in the past 3 months.

^c Indwelling devices (e.g., tracheotomies, central lines, urinary catheters, orthopedic external fixators) that were in place at least 48 h prior to VRE isolation.

^d Defined as length of hospital stay of >2 days before VRE isolation.

^e Penicillins include β -lactam/ β -lactamase inhibitor combinations.

^f Defined as elevation of creatinine to 50% or more above baseline.

^g Defined as the presence of at least 1 of the following conditions: (i) transaminases doubled compared to baseline value; (ii) INR above 1.5 without exposure to anticoagulants; and (iii) total bilirubin tripled compared to baseline.

^h Defined as an antibiotic demonstrating *in vitro* susceptibility to the VRE pathogen that was administered in the 14 days following the VRE culture.

ⁱ Defined by sustained VRE bacteremia at the time of switching therapy.

nation with study antimicrobials was rifampin (4 cases in the daptomycin group, 1 in the linezolid group, 3 in the β -lactam group), followed by aminoglycosides (1 in the daptomycin group, 3 in the linezolid group, 2 in the β -lactam group), tigecycline (3 in the linezolid group, 3 in the β -lactam group), and ceftriaxone-ceftaxime (3 in the β -lactam group). Each therapy was rarely changed to another active antimicrobial, and the frequency of changing effective therapeutic agents was similar in the three treatment groups (Table 1). No difference was noted among each study group with regard to switching due to treatment failure. Time to initiation of effective therapy was longer in the linezolid group than the daptomycin or β -lactams group (Table 1).

In bivariate analysis, in-hospital mortality among the daptomycin group was significantly higher ($n = 25$ patients [45%]) than in the linezolid ($n = 28$ [25%]) ($P = 0.01$) or β -lactams group ($n = 11$ [19%]) ($P = 0.01$). Among patients with bacteremia due to VR *E. faecium*, the difference between the rates of in-hospital mortality in the daptomycin and linezolid groups remained significant ($n = 22$ [46%] versus $n = 23$ [26%], $P = 0.02$). The bivariate rates were not significantly different between the daptomycin and β -lactam groups among patients with VR *E. faecium* bacteremia ($n = 22$ [46%] versus $n = 1$ [33%], $P = 1.0$), although the number of patients who received β -lactams was small ($n = 3$). Among patients with bacteremia due to VR *E. faecalis*, in-hospital mortality did not differ among the groups (daptomycin, linezolid, β -lactam groups, $n = 3$ [38%], $n = 5$ [21%], $n = 10$ [19%]; $P > 0.05$ for each comparison between 2 groups). In bivariate analysis, there was no statistical difference observed among each treatment group with regard to mortality within 3 months after discharge ($n = 5$ [16%] versus $n = 12$ [15%] versus $n = 2$ [4%]), LOS after culture, excluding those who died (median, 11 days [interquartile range (IQR), 4 to 12] versus 13 [7 to 26] versus 10 [6 to 17]), time to eradication of bacteremia (median of 37 h [IQR, 22 to 69] versus 40 [20 to 89] versus 52 [30 to 73]), or multiple isolations of the same species of VRE from the

blood of the same patient within 1 week following initial positive blood culture ($n = 31$ [55%] versus $n = 77$ [69%] versus $n = 35$ [63%]).

In the cohort of patients with immunocompromising conditions and/or hematologic malignancy, the mortality rates among patients in the daptomycin and linezolid groups were similar, but both were greater than the mortality rate in the β -lactam group (number [%] of in-hospital mortalities for the daptomycin, linezolid, and β -lactam groups, respectively: 18 [67%], 14 [45%], 2 [17%]; daptomycin versus linezolid, $P = 0.12$; daptomycin versus β -lactams, $P = 0.01$; linezolid versus β -lactams, $P = 0.16$). The differences in mortality were not statistically significant in the cohort excluding those patients with immunocompromising conditions or hematologic malignancy (daptomycin, linezolid, and β -lactam groups: 7 [24%], 14 [17%], and 9 [20%], respectively; $P > 0.05$). In the cohort of patients with indwelling devices at the time of VRE isolation, the mortality rate among patients in the daptomycin group was greater than the mortality rate in the linezolid group and β -lactam group (number [%] of in-hospital mortalities for the daptomycin, linezolid, and β -lactam group, respectively: 20 [49%], 24 [25%], and 10 [20%]; daptomycin versus linezolid, $P = 0.01$; daptomycin versus β -lactams, $P = 0.01$; linezolid versus β -lactams, $P = 0.68$). The differences in mortality were not significant in the cohort excluding those patients with indwelling devices (daptomycin, linezolid, and β -lactam groups: 5 [36%], 4 [27%], and 1 [13%], respectively; $P > 0.05$). In the cohort of patients who had surgery or invasive procedures in the prior 6 months, the mortality rate among patients in the daptomycin group was greater than the mortality rate in the linezolid group and β -lactam group (number [%] of in-hospital mortalities for the daptomycin, linezolid, and β -lactam groups, respectively: 23 [47%], 20 [24%], and 9 [24%]; daptomycin versus linezolid, $P = 0.01$; daptomycin versus β -lactams, $P = 0.04$; linezolid versus β -lactams, $P = 1.0$). The differences in mortality were not significant in the cohort, excluding those patients with indwelling

TABLE 2 Multivariate analysis and propensity score predicting the likelihood of receipt of one of the therapeutic classes for bacteremia due to VRE^a

Variable	Whole-study cohort						Cohort with hospital cost data					
	DAP vs LZD		DAP vs BL		LZD vs BL		DAP vs LZD		DAP vs BL		LZD vs BL	
	P value	PS value	P value	PS value	P value	PS value	P value	PS value	P value	PS value	P value	PS value
Not being diabetic	0.11	0.66					0.08	0.76				
Hematologic malignancy	<0.01	2.06										
Absence of indwelling device ^b at VRE isolation	0.03	1.14					0.03	1.10				
Focus unknown VRE bacteremia	0.01	1.53										
Hospital-acquired ^c VRE	<0.01	1.32	<0.01	1.79					<0.01	1.64		
Invasive procedure or surgery in the past 3 mo	0.02	1.29	0.01	1.71								
Age <65 yrs	0.11	0.70	0.12	0.86			0.04	0.90	0.11	0.83		
Not on chronic hemodialysis			0.19	0.72								
No chronic skin ulcers			0.13	0.87					0.19	0.69		
Non-African-American race			0.06	1.21	0.04	0.97					0.06	0.98
VRE monobacteremia ^d			0.02	1.22	0.09	0.62			0.06	0.93	0.05	0.75
Neurologic diseases							0.02	1.07				
No neurologic diseases					<0.01	1.13					<0.01	1.15
ICU stay at the time of VRE isolation					0.01	0.97					<0.01	1.07

^a BL, β -lactam; DAP, daptomycin; ICU, intensive care unit; IQR, interquartile range; LZD, linezolid; LOS, length of hospital stay; LTICF, long-term care facility; PS, propensity score; SIRS, systemic inflammatory response syndrome. PS value is equal to β -coefficient.

^b Indwelling devices (e.g., tracheotomies, central lines, urinary catheters, orthopedic external fixators) that were in place at least 48 h prior to VRE isolation.

^c Defined as length of hospital stay of >2 days before VRE isolation.

^d Absence of bacteremia due to organism other than VRE within 3 days of VRE bacteremia.

devices (daptomycin, linezolid, and β -lactam groups: 8 [29%], 2 [29%], and 2 [11%], respectively; $P > 0.05$). In the cohort of patients with an unknown primary source of VRE bacteremia, the differences in mortality were not significant among treatment groups (daptomycin, linezolid, and β -lactam group: 5 [50%], 2 [29%], and 2 [67%], respectively; $P > 0.05$).

Three multivariate models were constructed to predict the likelihood of receipt of one of the therapeutic classes compared to another class (Table 2). Based on these models, propensity scores were developed, and matched comparisons between treatment groups were conducted as described in Materials and Methods.

After controlling for time to effective therapy and VRE species (VR *E. faecalis* versus VR *E. faecium*), differences in mortality and LOS following VRE isolation were no longer significant as a function of treatment group (Table 3). However, median LOS following VRE bacteremia, excluding deaths, was longer in the linezolid group than in the β -lactam group ($P = 0.05$).

Sixteen (46%) of 35 patients who received 6 mg/kg daptomycin and 9 (43%) of 21 patients who received >6 mg/kg daptomycin (11 cases, 8 mg/kg; 9 cases, 10 mg/kg; 1 case, 12 mg/kg) died in the hospital ($P = 1.0$). Abnormal creatinine phosphokinase (CPK) levels (>350 U/liter) were recorded in 2 of 38 patients (5%) with recorded CPK values in the daptomycin group, in 11 of 35 (31%) in the linezolid group, and 3 of 9 (33%) in the β -lactam group (daptomycin versus linezolid, $P = 0.005$; daptomycin versus β -lactams, $P = 0.04$). Eight of 52 patients with medical records available in the daptomycin group were on statins (15%), as were 38 of 109 (35%) in the linezolid group and 24 of 57 (42%) in the β -lactam group (daptomycin versus linezolid, $P = 0.02$; daptomycin versus β -lactams, $P < 0.01$). Abnormal CPK levels developing after initiation of antibiotics were recorded in 1 patient in the daptomycin group (919 U/liter). Thrombocytopenia ($<100 \times 10^9$ platelets/liter) present at baseline or developing after initiation of antibiotics was reported in 14 of 39 (36%) patients in the dap-

TABLE 3 Multivariate analysis of clinical outcomes of bacteremia due to VRE as a function of type of antimicrobial therapy^a

Variable	Value						Multivariate analysis ^b		
	Model 1: daptomycin ($n = 39$) vs linezolid ($n = 39$)		Model 2: daptomycin ($n = 24$) vs β -lactams ($n = 24$)		Model 3: linezolid ($n = 49$) vs β -lactams ($n = 49$)		Comparison of treatments	OR ^c (95% CI)	P value
	DAP	LZD	DAP	BL	LZD	BL			
No. (%) of in-hospital deaths	16 (41)	12 (30.8)	8 (33.3)	5 (20.8)	9 (18.4)	9 (18.4)	Model 1	1.54 (0.59–4.02)	0.38
							Model 2	0.47 (0.05–4.9)	0.53
							Model 3	1.12 (0.31–4.03)	0.87
Median length of stay after VRE bacteremia (excluding deaths) in days (IQR)	11 (7–20)	13 (7–24)	12 (8–19)	9 (7–21)	17 (8–28)	9 (6–17)	Model 1	0.88 (0.48–1.32)	0.36
							Model 2	1.25 (0.64–2.97)	0.40
							Model 3	1.32 (1.0–2.56)	0.05

^a BL, β -lactams; DAP, daptomycin; IQR, interquartile range; LZD, linezolid; OR, odds ratio; CI, confidence interval. Each model was matched for propensity score (likelihood to receive daptomycin [models 1 and 2] or linezolid [model 3]) for the distance matrix of 0.5 in a 1:1 ratio. In the entire cohort, 39 (69.6%) subjects within the daptomycin group were matched to 39 (34.8%) within the linezolid group; 24 (42.9%) subjects within the daptomycin group were matched to 24 (42.1%) within the β -lactam group; and 49 (43.8%) subjects within the linezolid group were matched to 49 (86%) within the β -lactam group.

^b Controlled VR *E. faecalis* isolation (models 2 and 3) and time to effective therapy (models 1 and 3).

^c Odds ratio for in-hospital death. The effect estimates for length of stay were reported as the multiplicative effect (the antilog of the β coefficient).

TABLE 4 Multivariate analysis of fiscal outcomes of bacteremia due to VRE as a function of type of antimicrobial therapy^a

Cost (U.S. dollars)							Multivariate analysis ^b		
Variable	DAP	LZD	DAP	BL	LZD	BL	Comparison of treatments	Multiplicative effect ^c (95% CI)	P value
	Model 1: daptomycin (<i>n</i> = 33) vs linezolid (<i>n</i> = 33)			Model 2: daptomycin (<i>n</i> = 23) vs β-lactams (<i>n</i> = 23)					
Median variable direct cost per day	1,330 (850-1,669)	979 (828-1,264)	1,357 (861-1,596)	900 (697-1,405)	906 (707-1,201)	819 (609-1,157)	Model 1	1.27 (1.06-1.53)	0.01
							Model 2	1.38 (0.98-1.95)	0.06
							Model 3	1.04 (0.85-1.29)	0.68
Median variable direct cost for duration of hospitalization	22,340 (13,535-80,808)	20,932 (12,007-73,983)	21,366 (13,188-52,940)	9,825 (4,772-49,180)	16,530 (7,716-42,010)	10,202 (4,858-36,836)	Model 1	1.45 (0.93-2.28)	0.10
							Model 2	2.44 (1.10-5.40)	0.03
							Model 3	0.89 (0.51-1.56)	0.68

^a BL, β -lactams; DAP, daptomycin; IQR, interquartile range; LZD, linezolid. Each model was matched for propensity score (likelihood to receive daptomycin [models 1 and 2] or linezolid [model 3]) for the distance matrix of 0.5 in a 1:1 ratio. In the financial data cohort, 33 (91.7%) subjects within the daptomycin group were matched to 33 (31.4%) within the linezolid group; 23 (63.9%) subjects in the daptomycin group were matched to 23 (41.8%) in the β -lactam group; and 46 (43.8%) subjects in the linezolid group were matched to 46 (83.6%) subjects in the β -lactam group.

^b Controlled for length of hospital stay prior to VRE isolation (models 1, 2, and 3), VRE *E. faecalis* isolation (models 2 and 3), and time to effective therapy (models 1 and 3).
^c The effect estimates for cost were reported as the multiplicative effect (the antilog of the β -coefficient).

tomycin group with platelet values available, 21 of 100 (21%) in the linezolid group, and 1 of 50 (2%) in the β -lactam group (daptomycin versus β -lactams, $P < 0.001$; linezolid versus β -lactams, $P < 0.01$). Newly developed thrombocytopenia, occurring after initiation of antibiotics, was reported in 4 of 100 (4%) patients in the linezolid group (median, 72×10^9 /liter; range, 50×10^9 /liter to 96×10^9 /liter).

The cohort with hospital cost data. There were few notable differences in the results of bivariate analyses between the hospital cost data cohort and the entire cohort. In the cost data cohort, the differences between the treatment groups with regard to the prevalence of patients with hematologic malignancy, with an immunosuppressive state, who had an unknown anatomic focus of bacteremia, and who were receiving chronic hemodialysis were not significant (see Table S1s in the supplemental material). In the daptomycin group, neurologic diseases were more frequent, and Charlson's weighted index comorbidity score was higher in the cohort with cost data than in the whole cohort. The differences in mortality among the treatment groups observed in the whole-cohort analysis were not significant in the hospital cost data cohort. Median variable direct cost per day was highest in the daptomycin group and lowest in the β -lactam group (daptomycin versus linezolid, $P = 0.01$; daptomycin versus β -lactams, $P < 0.01$; linezolid versus β -lactams, $P < 0.01$).

Three multivariate models were constructed to predict the likelihood of receipt of one of the therapeutic classes, and propensity score matched comparisons between treatment groups were conducted as described in Materials and Methods (Table 2).

After controlling for time to effective therapy, VRE species (VR *E. faecalis* versus VR *E. faecium*), and LOS prior to VRE isolation, therapy with daptomycin was associated with higher median variable direct cost per day than therapy with linezolid ($P = 0.01$) and with higher median variable direct cost for the duration of hospitalization than the β -lactam group ($P = 0.03$) (Table 4).

DISCUSSION

Despite the significant differences in in-hospital mortality among each treatment group in bivariate analysis, differences in mortality were not significant after matching on propensity score and controlling for time to effective therapy and VRE species (VR *E. faecalis* versus VR *E. faecium*). The higher mortality in bivariate analysis within the daptomycin group may be explained by the fact that this population was more likely to have been immunocompromised, have had hematologic malignancy, have had indwelling devices, and have required invasive procedures and/or surgeries. This higher mortality rate in the bivariate analysis in the daptomycin group was likely due in part to "confounding by indication," i.e., patients with immunocompromising conditions and/or hematologic malignancies were more likely to die and were more likely to receive daptomycin. These differences were accounted for, in part, in multivariate analyses, where no differences in mortality among treatment groups were identified. Our results are in accordance with previous studies which compared daptomycin to linezolid for treatment of bacteremia due to VRE (15–17): these reports did not find significant differences in mortality among patients treated with daptomycin or linezolid.

Recently published meta-analyses revealed increased survival with linezolid compared to that with daptomycin (18, 19). One explanation for the differences in the findings in these studies compared to the current one is that these prior studies included

patients treated with daptomycin at a dose of less than 6 mg/kg. Despite their increased sample size, these meta-analyses were able to control only for those confounding factors that were addressed within the individual trials which were included. Due to the smaller sample size of the individual trials, specific confounders, including some markers of illness severity, may not have achieved sufficient statistical significance to merit inclusion in individual study results and thus would not have been accounted for in the meta-analyses. In general, sicker patients were included in the daptomycin-treated groups in the individual studies that made up the recent meta-analyses. In the current study, there was no statistical difference observed among each treatment group with regard to mortality within 3 months after discharge, LOS after culture (excluding subjects who died), time to eradication of bacteremia, or recurrent isolation of the same species of VRE from the blood of the same patient within 1 week following initial blood culture positivity. Although there was an increase of in-hospital mortality among daptomycin-treated patients in bivariate analysis, the magnitude of the association moved toward 1 in multivariable analysis. It is possible that the differences in the findings between this study and the meta-analyses may be due to residual confounding pertaining to illness severity in the individual studies included in the meta-analyses as well as in the meta-analyses themselves.

In our health system, VR *E. faecalis* accounts for a relatively high proportion of VRE (3), and the majority (97%) of isolated VR *E. faecalis* isolates are susceptible to ampicillin. The high proportion of VR *E. faecalis* in this study allowed for the comparison of β -lactam therapy to daptomycin and linezolid therapy. Such comparisons have not been previously performed. We previously reported that VR *E. faecalis* bacteremia was independently associated with decreased in-hospital mortality compared to VR *E. faecium* (20). In this study, patients with VR *E. faecalis* bacteremia also had decreased in-hospital mortality compared to that of VR *E. faecium* ($n = 18$ cases [20.9%] versus $n = 46$ cases [33.1%], $P = 0.07$). Therefore, bacteremia due to VR *E. faecalis* as opposed to VR *E. faecium* was controlled for in the multivariate outcomes analyses.

In a prior study, vancomycin-resistant enterococcal bacteremia was reported to be associated with increased overall hospital charges in addition to increased mortality and length of stay (21). In the current study, in a cohort analysis that excluded cancer institute patients, median variable direct cost per day was highest in the daptomycin group, followed by in the linezolid and β -lactam groups. In multivariate analysis, the difference in cost between the daptomycin and linezolid groups remained significant even after subjects were matched by propensity score. The higher costs in the daptomycin group than in the β -lactam and linezolid groups might have been due, in part, to higher acquisition costs (particularly for daptomycin doses of >6 mg/kg) and infusion-related costs of daptomycin. Due to its high bioavailability, linezolid was used as an oral treatment option for VRE bacteremia; more than half (57 patients [50.9%]) of the linezolid group received linezolid orally. After length of hospital stay prior to VRE isolation and time to effective therapy were controlled for, median variable direct costs for duration of hospitalization were similar between the daptomycin and linezolid groups.

The optimal dose of daptomycin for the treatment of bacteremia due to VRE remains unclear. Even though this study was not designed specifically to evaluate clinical outcomes as a function of

daptomycin dose, there was no difference in mortality observed between higher (>6 mg/kg) and lower (6 mg/kg) doses of daptomycin. A previous study comparing higher (>6 mg/kg) and lower (≤ 6 mg/kg) doses of daptomycin for the treatment of bacteremia due to VRE did not report a difference in time to microbiological cure (22). A higher daptomycin dose might be beneficial in certain situations, such as endovascular infections (4).

We used all-cause mortality instead of infection-related mortality to avoid abstractor biases that might have been associated with determining infection-related mortality. We included patients with single sets of blood cultures positive for VRE. The proportion of contamination/colonization did not differ among treatment groups (Table 1). Treatment agents were not delivered to patients in a randomized fashion. The confounding inherent in observational studies comparing different antimicrobial therapies was addressed in part, using propensity score analyses. However, even after matching on propensity score and controlling for differences between treatment groups, it is possible that residual confounding remained. After propensity score matching analyses were performed, daptomycin still was associated with a trend toward increased mortality (41% versus 31% against linezolid, and 33% versus 21% against β -lactams), although this was not statistically insignificant. The matching resulted in decreased sample sizes.

Due to the lack of availability of direct hospital costs for patients who were admitted to the cancer institute, two separate cohorts for analyses were used. The cohort with hospital cost data excluded cancer institute patients, limiting the generalizability of results. Another limitation was that combination therapy was used for only a small fraction of study subjects, and, thus, definitive evaluations of the impact of combination therapy on outcomes of patients with bacteremia due to VRE could not be conducted.

In conclusion, this large study revealed that daptomycin, linezolid, and β -lactams were similarly efficacious in the treatment of bacteremia due to VRE. In order to provide the most effective therapy for patients with bacteremia due to VRE, future studies should address issues pertaining to treatment duration, optimal dosing of daptomycin, and the impact and role of combination therapy. In addition, analyses focusing on special populations, such as patients with hematologic malignancy, are warranted.

ACKNOWLEDGMENTS

This work was supported in part by Pfizer, Inc., and Cubist, Pharmaceuticals.

K.S.K. is supported by the National Institute of Allergy and Infectious Diseases (NIAID), DMID protocol number 10-0065. K.S.K. is a speaker and consultant and received grant support from Pfizer and Cubist. M.J.R. is supported by the National Institutes of Allergy and Infectious Diseases and has been a speaker or consultant and has received grant support from Astellas, Cubist, Forest, and Rib-X. E.T.M. is supported by the National Institutes of Allergy and Infectious Diseases (5K01AI099006-02) and has received grant support from Pfizer. All other authors report no potential conflicts.

REFERENCES

1. Arias CA, Mendes RE, Stilwell MG, Jones RN, Murray BE. 2012. Unmet needs and prospects for oritavancin in the management of vancomycin-resistant enterococcal infections. *Clin. Infect. Dis.* 54(Suppl 3):S233–S238.
2. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK. 2008. NHSN annual update: antimicrobial-resistant patho-

- gens 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. <http://dx.doi.org/10.1086/591861>.
3. Hayakawa K, Marchaim D, Vidaillac C, Lephart P, Pogue JM, Sunkara B, Kotra H, Hasan A, Shango M, Yerramalla Y, Osunlana AM, Chopra T, Dhar S, Salimnia H, Rybak MJ, Kaye KS. 2011. Growing prevalence of vancomycin-resistant *Enterococcus faecalis* in the region with the highest prevalence of vancomycin-resistant *Staphylococcus aureus*. *Infect. Control Hosp. Epidemiol.* 32:922–924. <http://dx.doi.org/10.1086/661599>.
 4. Arias CA, Murray BE. 2008. Emergence and management of drug-resistant enterococcal infections. *Expert Rev. Anti Infect. Ther.* 6:637–655. <http://dx.doi.org/10.1586/14787210.6.5.637>.
 5. Clinical and Laboratory Standards Institute. 2009. Performance standards for antimicrobial susceptibility testing; nineteenth informational supplement. Approved standard M100-S19. CLSI, Wayne, PA.
 6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 40:373–383. [http://dx.doi.org/10.1016/0021-9681\(87\)90171-8](http://dx.doi.org/10.1016/0021-9681(87)90171-8).
 7. Bion JF, Edlin SA, Ramsay G, McCabe S, Ledingham IM. 1985. Validation of a prognostic score in critically ill patients undergoing transport. *Br. Med. J.* 291:432–434. <http://dx.doi.org/10.1136/bmj.291.6493.432>.
 8. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL. 2008. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit. Care Med.* 36:296–327. <http://dx.doi.org/10.1097/01.CCM.0000298158.12101.41>.
 9. Centers for Disease Control and Prevention. 2014. Central line-associated bloodstream infection (CLABSI) event. CDC, Atlanta, GA. http://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.
 10. Horan TC, Andrus M, Dudeck MA. 2008. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am. J. Infect. Control* 36:309–332. <http://dx.doi.org/10.1016/j.ajic.2008.03.002>.
 11. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. 2009. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 49:1–45. <http://dx.doi.org/10.1086/599376>.
 12. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. 1963. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. *JAMA* 185:914–919.
 13. Conceicao N, de Oliveira Cda C, da Silva LE, de Souza LR, de Oliveira AG. 2012. Ampicillin susceptibility can predict *in vitro* susceptibility of penicillin-resistant, ampicillin-susceptible *Enterococcus faecalis* isolates to amoxicillin but not to imipenem and piperacillin. *J. Clin. Microbiol.* 50:3729–3731. <http://dx.doi.org/10.1128/JCM.01246-12>.
 14. Carmeli Y, Troillet N, Karchmer AW, Samore MH. 1999. Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. *Arch. Intern. Med.* 159:1127–1132. <http://dx.doi.org/10.1001/archinte.159.10.1127>.
 15. Crank CW, Scheetz MH, Brielmaier B, Rose WE, Patel GP, Ritchie DJ, Segreti J. 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. <http://dx.doi.org/10.1016/j.clinthera.2010.09.008>.
 16. Mave V, Garcia-Diaz J, Islam T, Hasbun R. 2009. Vancomycin-resistant enterococcal bacteraemia: is daptomycin as effective as linezolid? *J. Antimicrob. Chemother.* 64:175–180. <http://dx.doi.org/10.1093/jac/dkp154>.
 17. Twilla JD, Finch CK, Usery JB, Gelfand MS, Hudson JQ, Broyles JE. 2012. Vancomycin-resistant enterococcus bacteremia: an evaluation of treatment with linezolid or daptomycin. *J. Hosp. Med.* 7:243–248. <http://dx.doi.org/10.1002/jhm.994>.
 18. Balli EP, Venetis CA, Miyakis S. 2014. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. *Antimicrob. Agents Chemother.* 58:734–739. <http://dx.doi.org/10.1128/AAC.01289-13>.
 19. Whang DW, Miller LG, Partain NM, McKinnell JA. 2013. Systematic review and meta-analysis of linezolid and daptomycin for treatment of vancomycin-resistant enterococcal bloodstream infections. *Antimicrob. Agents Chemother.* 57:5013–5018. <http://dx.doi.org/10.1128/AAC.00714-13>.
 20. Hayakawa K, Marchaim D, Martin ET, Tiwari N, Yousuf A, Sunkara B, Pulluru H, Kotra H, Hasan A, Bheemreddy S, Sheth P, Lee DW, Kamatam S, Bathina P, Nanjireddy P, Chalana IK, Patel S, Kumar S, Vahia A, Ku K, Yee V, Swan J, Pogue JM, Lephart PR, Rybak MJ, Kaye KS. 2012. Comparison of the clinical characteristics and outcomes associated with vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *E. faecium* bacteremia. *Antimicrob. Agents Chemother.* 56:2452–2458. <http://dx.doi.org/10.1128/AAC.06299-11>.
 21. Song X, Srinivasan A, Plaut D, Perl TM. 2003. Effect of nosocomial vancomycin-resistant enterococcal bacteremia on mortality, length of stay, and costs. *Infect. Control Hosp. Epidemiol.* 24:251–256. <http://dx.doi.org/10.1086/502196>.
 22. King EA, McCoy D, Desai S, Nyirenda T, Bicking K. 2011. Vancomycin-resistant enterococcal bacteraemia and daptomycin: are higher doses necessary? *J. Antimicrob. Chemother.* 66:2112–2118. <http://dx.doi.org/10.1093/jac/dkr255>.