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Systematic Review and Meta-Analysis of Linezolid and Daptomycin for Treatment of Vancomycin-Resistant Enterococcal Bloodstream Infections

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Bloodstream infections due to vancomycin-resistant enterococci (VRE-BSI) result in substantial patient mortality and cost. Daptomycin and linezolid are commonly prescribed for VRE-BSI, but there are no clinical trials to determine optimal antibiotic selection. We conducted a systematic review for investigations that compared daptomycin and linezolid for VRE-BSI. We searched Medline from 1966 through 2012 for comparisons of linezolid and daptomycin for VRE-BSI. We included searches of EMBASE, clinicaltrials.gov, and national meetings. Data were extracted using a standardized instrument. Pooled odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using a fixed-effects model. Our search yielded 4,243 publications, of which 482 contained data on VRE treatment. Most studies (452/482) did not present data on BSI or did not provide information on linezolid or daptomycin. Among the remaining 30 studies, 9 offered comparative data between the two agents. None were randomized clinical trials. There was no difference in microbiologic ($n = 5$ studies, 517 patients; OR, 1.0; 95% CI, 0.4 to 1.7; $P = 0.95$) and clinical ($n = 3$ studies, 357 patients; OR, 1.2; 95% CI, 0.7 to 2.0; $P = 0.7$) cures between the two antibiotics. There was a trend toward increased survival with linezolid compared to daptomycin treatment ($n = 9$ studies, 1,074 patients; OR, 1.3; 95% CI, 1.1 to 1.8; $I^2 = 0$ [where I^2 is a measure of inconsistency]), but this did not reach statistical significance ($P = 0.054$). There are limited data to inform clinicians on optimal antibiotic selection for VRE-BSI. Available studies are limited by small sample size, lack of patient-level data, and inconsistent outcome definitions. Additional research, including randomized clinical trials, is needed before conclusions can be drawn about treatment options for VRE therapy.

Bloodstream infections due to vancomycin-resistant enterococcal species (VRE-BSI) are a rapidly growing problem in hospitals, with life-threatening consequences for patients (1–5). Despite infection prevention and control efforts, U.S. hospitalizations associated with VRE doubled between 2000 and 2006 and appear to be further increasing (1–6). National surveys of U.S. intensive care units (ICUs) indicate that VRE represented <1% of enterococcal isolates in 1990, but more recent data suggest that they now exceed 30% (1–4).

VRE-BSI primarily affect the most vulnerable patient populations, including postsurgical and trauma patients, complex internal medicine patients, and those who have undergone organ transplantation, especially liver transplantation (7–12). VRE-BSI are associated with significant mortality in cohorts of hematopoietic stem cell transplant recipients, liver transplant patients, oncology patients, and other inpatient populations (11–19). Importantly, effective antibiotic therapy and shorter duration of bacteremia are associated with lower mortality in patients with VRE-BSI (11, 19–22).

Newer antimicrobial agents with activity against VRE (daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline) provide much-needed therapeutic options for VRE-BSI, but there are limited data to inform clinicians as to which among these drugs are most effective for VRE-BSI. Two phase III clinical trials for VRE-BSI were started but were subsequently aborted due to enrollment difficulties (23, 24). To our knowledge, there are no further plans to initiate phase II or phase III clinical trials for VRE-BSI.

Among currently available agents with activity against VRE, daptomycin and linezolid have been used most frequently for VRE-BSI treatment (22, 25–30). Daptomycin is a cyclic lipopeptide with a broad spectrum of activity against Gram-positive organisms, including VRE (31, 32). Higher doses of daptomycin (≥8 mg/kg) are thought to improve clinical outcomes from VRE-BSI (33, 34). Linezolid is an oxazolidinone that inhibits bacterial protein synthesis by inhibiting ribosomal complex formation. Its spectrum of activity against Gram-positive organisms includes most isolates of VRE (35). However, marrow toxicity and peripheral neuropathy from prolonged linezolid use are considered important limitations, particularly in bone marrow transplant patients with VRE-BSI (26, 36). One observational investigation suggested that linezolid was associated with a survival advantage for VRE-BSI (37); however, there have been no attempts to systematically review the literature on VRE-BSI outcomes focusing on antimicrobial therapy. We therefore conducted a systematic review and meta-analysis to quantify differences in clinical outcomes from VRE-BSI treated with daptomycin or linezolid.

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MATERIALS AND METHODS

Search strategy and study selection. We performed a literature search of Medline from 1966 to December 2012 and of EMBASE from 1980 to December 2012 to find published manuscripts evaluating linezolid and daptomycin for treatment of VRE-BSI in patients. We limited studies to those in English and using human subjects and searched for the following terms: "vancomycin-resistant," "enterococcus," "*faecalis*," "*faecium*," and "VRE." In addition, we examined the references of all identified articles to look for additional relevant articles. We reviewed the abstracts from the annual meetings of the Infectious Disease Society of America (IDSA), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) from 1986 to 2012.

Abstracts from each reference from our electronic search were independently reviewed for relevance by two physician investigators (D. W. Whang and J. A. McKinnell). Studies were selected for full review if they reported primary data from patients with VRE-BSI treated with either linezolid or daptomycin. Studies that did not separate data on outcomes between vancomycin-sensitive and vancomycin-resistant enterococcal infections were excluded. Studies that reported only on treatment experience with a single agent, providing no comparative data, were not included. In the final analysis, only retrospective cohort investigations comparing patients treated with linezolid against those treated with daptomycin were included. There were no exclusions for different types of patients. The intervention of interest was antibiotic selection. The comparison groups were linezolid- and daptomycin-treated patients. The outcome of interest was mortality, as defined by the study investigators. The MOOSE criteria were used to evaluate study quality (38).

Data extraction, data analysis, and statistical methods. Each manuscript underwent independent, blinded, double-data extraction by two reviewers (D. W. Whang and N. M. Partain) using a standardized instrument. Discrepancies in data extraction underwent arbitration by a third reviewer (J. A. McKinnell), and consensus was obtained by oral discussion. Data collected from each study included year of study, number of patients, definition of infection, dose of daptomycin and linezolid used, microbiologic cure, clinical cure, and mortality. Infections, mortality, microbiologic cure rates, and clinical cure rates were defined according to descriptions provided by each study.

Additional data were collected about the patient cohorts when present, including gender, ethnicity, age, ICU versus ward-level care, comorbid conditions, source of bacteremia, vasopressor use, malignancy, organ or stem cell transplant, immunosuppression, concomitant bacteremia, and infectious disease consultation. All-cause mortality, microbiologic cure rates, and clinical cure rates were the primary outcome measures used in this meta-analysis.

Odds ratios (OR) for mortality were calculated for each study. Mantel-Haenszel statistical methods were used to calculate the pooled odds ratios, 95% confidence intervals (CI), and the associated *P* values of each risk factor using a fixed-effects model. We analyzed heterogeneity in publication using the I^2 measure of inconsistency. We utilized a DerSimonian and Laird random-effects model to generate confidence intervals. Studies were not additionally weighted by study quality. We present a forest plot of data from each individual study (39, 40).

RESULTS

Our search yielded 4,243 publications, of which 482 contained data on treatment of VRE (Fig. 1). The majority of investigations ($n = 452$) did not have data on BSI as a site of infection. Among the 30 studies containing data on outcomes of VRE-BSI treated with linezolid or daptomycin, nine investigations provided comparative data on linezolid and daptomycin and were included in the final analysis (22, 26–30, 37, 41, 42). Eight of the studies were based in the United States, and one study was based in Taiwan.

The nine investigations that were included in our final analysis

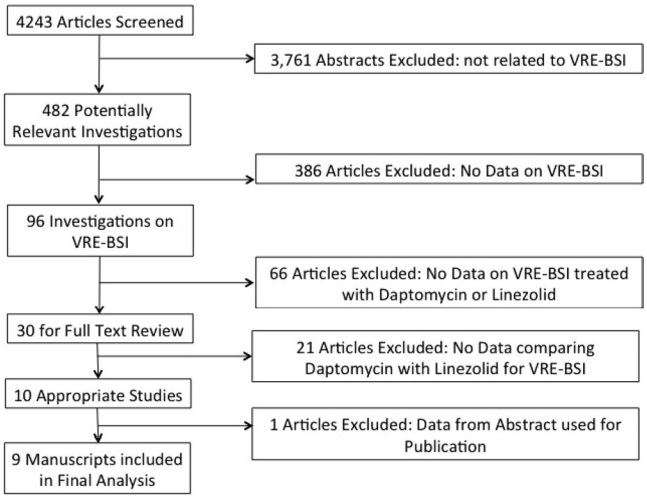

FIG 1 Flow chart representing the study selection process and reasons for exclusion.

reported on 1,074 patients treated for VRE-BSI. The investigations included in our analysis differed in their cohorts and how they defined VRE-BSI (Table 1). Three investigations required at least two positive cultures for VRE to define a case of VRE-BSI (28, 30). The remaining investigations required only one positive bloodstream culture, with two studies additionally using criteria of the Centers for Disease Control and Prevention for BSI (26, 27). Studies also differed in their definition of mortality. Three investigations used 30-day all-cause mortality, one investigation reported 14-day mortality, two investigations used inpatient all-cause mortality, two investigations used all-cause mortality at end of therapy, and one manuscript used all-cause mortality 7 days after end of therapy. Linezolid was uniformly given at a dose of 600 mg every 12 h; daptomycin was usually given at 6 mg/kg, but doses ranged from 3.4 mg/kg to 10.4 mg/kg (Table 1).

Comparisons of microbiologic cure, clinical cure, and mortality between daptomycin and linezolid are reported in Table 2. Our meta-analysis suggests that linezolid therapy is associated with increased survival for patients with VRE-BSI ($n = 9$ studies, 1,074 patients; OR, 1.3; 95% CI, 1.0 to 1.8; $I^2 = 0$), but this did not reach statistical significance ($P = 0.053$) (Fig. 2). Only one study demonstrated a statistically significant association between daptomycin and mortality (37). Outcomes were similar between linezolid and daptomycin treatments for microbiologic cure ($n = 5$ studies, 517 patients; OR, 1.0; 95% CI, 0.4 to 1.7; $P = 0.95$) and clinical cure ($n = 3$ studies, 357 patients; OR, 1.2; 95% CI, 0.5 to 2.1; $P = 0.68$; $I^2 = 0$) (Table 3).

DISCUSSION

VRE-BSI is a potentially life-threatening complication for hospitalized patients, particularly the immunocompromised. Effective antibiotic therapy has been shown to reduce mortality from VRE-BSI (13). However, the high attributable mortality associated with VRE-BSI in cohorts of hematopoietic stem cell transplant recipients, liver transplant patients, oncology patients, and inpatient populations (11–19) warrants an examination of the literature to examine which therapies may be associated with improved clinical outcomes in these vulnerable populations.

Our systematic review provides an important assessment of

TABLE 1 Investigations that compared daptomycin and linezolid therapy for VRE-BSI within a single cohort

Reference	Cohort/definition of VRE-BSI	Treatment[f]	Location	Date of study (yr)	Study size (no. of patients)	Linezolid dose (mg BID)[g]	Mean daily daptomycin dose (mg/kg [range])	Overall cure rate (%)		Mortality (%)	Mortality end point
								Clinical	Microbiologic		
Bio (30)	2 Positive cultures[a]	D or L (>3 days)	Philadelphia, PA	2004–2008	84	600	6 (3.7–8.8)[i]	52	88	36	Within 7 days after the end of therapy
Crank (28)	2 Positive cultures[b,c]	D or L	Chicago, Il	2003–2007	101	600	5.5[j]	NA	NA	41	Inpatient all-cause mortality
Dubrovskaya (37)	1 Positive culture	D or L	New York, NY	2005–2007	80	NA[h]	6 (4–9)	NA	97	23	All-cause mortality at the end of therapy
Furuya (41)	1 Positive culture	D or L	New York, NY	2004–2005	54	NA	5.7 (3.9–7.9)	NA	91	43	All cause mortality at the end of therapy
Kraft (22)	1 Positive culture[d]	D or L (>2 days)	Ann Arbor, MI	2004–2007	72	NA	NA	76	NA	24	30-day all-cause mortality
Lu (42)	2 Positive cultures[e]	NA	Taipei, Taiwan	2003–2010	149	NA	NA	NA	NA	48	14-day mortality[k]
Mave (27)	1 Positive culture; CDC criteria for BSI	D or L	New Orleans, LA	2003–2007	98	600	6	NA	89	22	Inpatient all-cause mortality
McKinnell (26)	1 Positive culture; CDC criteria for BSI	NA	Birmingham, AL	2005–2008	235	NA	NA	NA	78	35	30-day all-cause mortality
Twilla (29)	1 Positive culture	D or L (>5 days)	Memphis, TN	2004–2009	201	600	6.1 (3.4–10.40)	74	94	20	30-day all-cause mortality

[a] Two blood cultures.
[b] Two blood cultures or one blood culture with a second culture from another site.
[c] Polymicrobial infections excluded.
[d] Hematology/bone marrow transplant.
[e] Febrile patient.
[f] D, daptomycin; L, linezolid.
[g] BID, twice daily.
[h] NA, not available. The information was not stated in the article.
[i] Value is the median (range).
[j] Information on other doses is as follows: 4 mg/kg, $n = 23$; 6 mg/kg, $n = 38$; 8 mg/kg, $n = 6$.
[k] 28-Day mortality was 60%.

TABLE 2 Results from each investigations comparing linezolid and daptomycin in terms of microbiologic cure, clinical cure and mortality

Reference	Cohort/definition of VRE-BSI	Antibiotic[f]	Clinical cure		Microbiologic cure		Mortality	
			No. of cured patients/no. of treated patients (%)	OR (95% CI)	No. of cured patients/no. of treated patients (%)	OR (95% CI)	No. of deaths/no. of treated patients (%)	OR (95% CI)
Bio (30)	2 Positive cultures[a]	D	22/37 (65)	1.7 (0.7–4.0)	32/37 (87)	0.8 (0.2–2.8)	12/37 (32)	0.8 (0.3–1.9)
		L (>3 days)	22/47 (50)		42/47 (90)		18/47 (38)	
Crank (28)	2 Positive cultures[b,c]	D	NA[g]	NA	NA	NA	31/67 (46)	2.1 (0.9–5.0)
		L	NA		NA		10/34 (29)	
Dubrovskaya (37)	1 Positive culture	D	NA	NA	39/40 (98)	1.0 (0.1–16.6)	13/40 (33)	3.4 (1.1–10.6)
		L	NA		39/40 (97)		5/40 (13)	
Furuya (41)	1 Positive culture	D	NA	NA	14/14 (100)	NC	5/14 (36)	0.7 (0.2–2.4)
		L	NA		35/40 (88)		18/40 (45)	
Kraft (22)	1 Positive culture[d]	D	33/43 (77)	1.1 (0.3–3.2)	NA	NA	10/43 (23)	0.9 (0.3–2.9)
		L (>2 days)	22/29 (76)		NA		7/29 (24)	
Lu (42)	2 Positive cultures[e]	D	NA	NA	NA	NA	11/29 (38)	1.2 (0.5–2.9)[h]
		L	NA		NA		22/64 (34)	
Mave (27)	1 Positive culture; CDC criteria for BSI	D	NA	NA	27/30 (90)	1.2 (0.3–4.9)	8/30 (27)	1.4 (0.5–3.8)
		L	NA		60/68 (88)		14/68 (21)	
McKinnell (26)	1 Positive culture; CDC criteria for BSI	D	NA	NA	61/86 (71)	0.5 (0.3–1.0)	25/61 (29)	3.3 (1.6–6.8)
		L	NA		86/104 (83)		18/104 (18)	
Twilla (29)	1 Positive culture	D	47/63 (75)	1.0 (0.5–2.1)	59/63 (94)	0.9 (0.3–3.1)	15/63 (24)	14. (0.7–2.9)
		L (>5 days)	102/138 (74)		130/138 (94)		25/138 (18)	

[a] Two blood cultures.
[b] Two blood cultures or one blood culture with a second culture from another site.
[c] Polymicrobial infections excluded.
[d] Hematology/bone marrow transplant.
[e] Febrile patient.
[f] D, daptomycin; L, linezolid.
[g] NA, not available. The information was not stated in the article.
[h] For daptomycin, 28-day mortality was 17/29 (59%); for linezolid it was 33/64 (52%).

available literature on selection of linezolid versus daptomycin for the treatment of VRE-BSI. Although we did not identify data from clinical trials of VRE-BSI, we found a trend toward an association between linezolid therapy and patient survival in the available literature. The association between linezolid and lower patient mortality than with daptomycin treatment reached statistical significance in one analysis by Dubrovskaya et al., which examined 80 patients in an academic medical center in New York (37).

Despite the objective results from our meta-analysis showing an association between linezolid and survival, we strongly caution that our findings should not be considered conclusive. There were relatively few investigations included in our analysis, and all were retrospective cohort analyses. Differences in definitions of mortality may further have introduced bias. Moreover, there was evidence of treatment selection bias in these investigations. Four investigations demonstrated a bias toward using daptomycin in patients with hematologic abnormalities (22, 26, 29, 30). As a result, some of the observed mortality difference between treatments may be a product of the confounding by indication where "sicker" patients were given daptomycin. One method to account

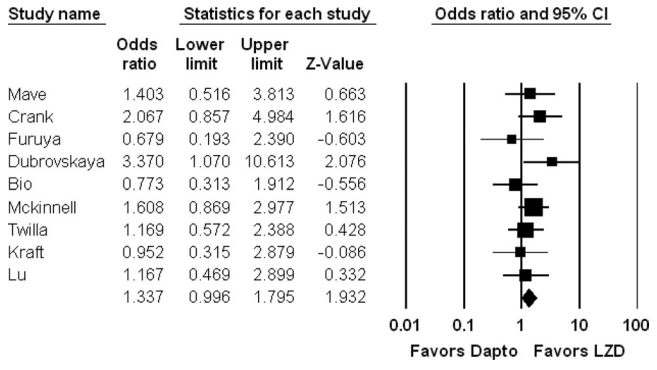

FIG 2 Meta-analysis comparing mortality in patients treated with linezolid versus daptomycin treatment for VRE-BSI. The forest plot shows results for overall mortality in patients treated with linezolid versus daptomycin. No weighting criteria were applied to the calculations. The overall trend is for improved survival with linezolid versus daptomycin (OR, 1.3), but this is not statistically significant ($P = 0.053$). Dapto, daptomycin; LZD, linezolid.

TABLE 3 Results of meta-analysis of studies comparing linezolid with daptomycin for the treatment of VRE-BSI

Outcome[a]	No. of studies	No. of patients	OR[b]	95% CI	*P* value
Mortality	9	1,074	1.3	0.996–1.8	0.053
Inpatient	4	333	1.7	1.1–2.8	0.08
30-Day	3	271	1.3	0.9–2.3	0.20
Microbiologic cure	5	517	1.0	0.4–1.7	0.95
Clinical cure	3	357	1.2	0.5–2.1	0.68

[a] Outcomes of linezolid versus daptomycin treatment were as defined by the investigation.
[b] Odds ratios greater than 1 favor linezolid treatment, and odds ratios less than 1 favor daptomycin treatment. For the paper by Lu et al. (42), the 14-day mortality numbers were used for the calculation of the mortality odds ratio. Analysis using the 28-day mortality was not significantly different.

for differences between treatment groups would be to conduct a patient-level quantitative analysis of all studies to assess the impact of host, organism, and treatment-related factors on mortality and clinical cure. This method of analysis has proven successful in investigations of other infectious syndromes, but patient-level data were not available from the investigations included in this review (43).

Though our data trended toward an association between linezolid therapy and survival, we did not observe an association between linezolid and microbiologic cure ($P = 0.95$). In nearly all investigations, microbiologic cure was defined relatively late in the course of disease, typically 7 to 14 days after VRE-BSI was diagnosed. In contrast to traditional measures of microbiologic cure, duration of bacteremia and probability of repeat positive blood culture while on therapy may be more sensitive measures of antibiotic activity and are thought to be an important predictor of mortality. Diazgranados and Jernigan presented a robust analysis showing a dose-response relationship between bacteremia duration and mortality using a Cox proportional hazards models (11). Bhavnani and colleagues reported that positive follow-up cultures were associated with mortality (odds ratio, 10.1; 95% CI, 2.2 to 46.7) (21). Similarly, Kraft et al. reported that bacteremia that persisted over multiple days was associated with significantly higher mortality (22). Among the studies included in our review, one investigation found a higher likelihood of repeat cultures positive for VRE while on daptomycin ($P = 0.01$) and higher recurrence of VRE while patients were on daptomycin ($P = 0.03$) (29). Alternatively, Crank et al. and Kraft et al. found no difference in duration of bacteremia between linezolid and daptomycin treatments (22, 28).

An important consideration of this literature review is that the majority of studies described daptomycin dosing at 6 mg/kg, with relatively few patients receiving higher doses of daptomycin (≥8 mg/kg). Higher doses of daptomycin are thought to improve clinical outcomes from VRE-BSI compared to traditional doses (33, 34). Among studies included in our final analysis, there is evidence from one investigation that lower doses of daptomycin were associated with recurrently positive cultures (29). There has been limited *in vitro* data, and emerging clinical data suggest that combination therapy for VRE-BSI with an effective antibiotic and a β-lactam may be more effective that effective antibiotics alone (44, 45). None of the investigations in our study adjusted for β-lactam adjunctive therapy for VRE.

In summary, our results suggest that there may be a mortality difference between daptomycin and linezolid for the treatment of VRE-BSI. However, the literature on VRE-BSI is quite limited. There were no clinical trials in our review of the literature. The available manuscripts include small-cohort analyses, affected by traditional limitations of retrospective studies. There were also significant differences in study design, and importantly daptomycin may have been underdosed. With the failure of two VRE-BSI clinical trials to enroll an adequate number of subjects, the low likelihood of having a gold-standard, prospective randomized clinical trial of VRE-BSI in the near future is concerning. Until such a trial is performed, we strongly believe that further retrospective analyses of VRE-BSI that control for important clinical predictors and utilize sensitive outcomes such as duration of bacteremia, likelihood of repeat positive cultures while on therapy, time to clinical cure, and traditional endpoints such as mortality will be critical to understanding the role of antibiotic choice for this increasingly common and potentially deadly infection (46).

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REFERENCES

1. **Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK.** 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.
2. **Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB.** 2004. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin. Infect. Dis. **39:**309–317.
3. **Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN.** 2007. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. Diagn. Microbiol. Infect. Dis. **58:**163–170.
4. **System NNIS.** 2004. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. Am. J. Infect. Control **32:**470–485.
5. **Reik R, Tenover FC, Klein E, McDonald LC.** 2008. The burden of vancomycin-resistant enterococcal infections in US hospitals, 2003 to 2004. Diagn. Microbiol. Infect. Dis. **62:**81–85.
6. **Ramsey AM, Zilberberg MD.** 2009. Secular trends of hospitalization with vancomycin-resistant enterococcus infection in the United States, 2000–2006. Infect. Control Hosp. Epidemiol. **30:**184–186.
7. **Orloff SL, Busch AM, Olyaei AJ, Corless CL, Benner KG, Flora KD, Rosen HR, Rabkin JM.** 1999. Vancomycin-resistant *Enterococcus* in liver transplant patients. Am. J. Surg. **177:**418–422.
8. **Kamboj M, Chung D, Seo SK, Pamer EG, Sepkowitz KA, Jakubowski AA, Papanicolaou G.** 2010. The changing epidemiology of vancomycin-resistant *Enterococcus* (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Biol. Blood Marrow Transplant. **16:**1576–1581.
9. **Weinstock DM, Conlon M, Iovino C, Aubrey T, Gudiol C, Riedel E, Young JW, Kiehn TE, Zuccotti G.** 2007. Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. Biol. Blood Marrow Transplant. **13:**615–621.
10. **Ghanem G, Hachem R, Jiang Y, Chemaly RF, Raad I.** 2007. Outcomes for and risk factors associated with vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* bacteremia in cancer patients. Infect. Control Hosp. Epidemiol. **28:**1054–1059.
11. **DiazGranados CA, Jernigan JA.** 2005. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J. Infect. Dis. **191:**588–595.
12. **Gearhart M, Martin J, Rudich S, Thomas M, Wetzel D, Solomkin J, Hanaway MJ, Aranda-Michel J, Weber F, Trumball L, Bass M, Zavala E, Steve Woodle E, Buell JF.** 2005. Consequences of vancomycin-resistant Enterococcus in liver transplant recipients: a matched control study. Clin. Transplant. **19:**711–716.
13. **Vergis EN, Hayden MK, Chow JW, Snydman DR, Zervos MJ, Linden PK, Wagener MM, Schmitt B, Muder RR.** 2001. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia: a prospective multicenter study. Ann. Intern. Med. **135:**484–492.
14. **Erlandson KM, Sun J, Iwen PC, Rupp ME.** 2008. Impact of the more-potent antibiotics quinupristin-dalfopristin and linezolid on outcome

measure of patients with vancomycin-resistant *Enterococcus* bacteremia. Clin. Infect. Dis. **46:**30–36.
15. **Garbutt JM, Ventrapragada M, Littenberg B, Mundy LM.** 2000. Association between resistance to vancomycin and death in cases of *Enterococcus faecium* bacteremia. Clin. Infect. Dis. **30:**466–472.
16. **Song JH, Ko KS, Suh JY, Oh WS, Kang CI, Chung DR, Peck KR, Lee NY, Lee WG.** 2008. Clinical implications of vancomycin-resistant *Enterococcus faecium* (VRE) with VanD phenotype and *vanA* genotype. J. Antimicrob. Chemother. **61:**838–844.
17. **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.
18. **Papanicolaou GA, Meyers BR, Meyers J, Mendelson MH, Lou W, Emre S, Sheiner P, Miller C.** 1996. Nosocomial infections with vancomycin-resistant *Enterococcus faecium* in liver transplant recipients: risk factors for acquisition and mortality. Clin. Infect. Dis. **23:**760–766.
19. **Camins BC, Farley MM, Jernigan JJ, Ray SM, Steinberg JP, Blumberg HM.** 2007. A population-based investigation of invasive vancomycin-resistant *Enterococcus* infection in metropolitan Atlanta, Georgia, and predictors of mortality. Infect. Control Hosp. Epidemiol. **28:**983–991.
20. Reference deleted.
21. **Bhavnani SM, Drake JA, Forrest A, Deinhart JA, Jones RN, Biedenbach DJ, Ballow CH.** 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.
22. **Kraft S, Mackler E, Schlickman P, Welch K, DePestel DD.** 2011. Outcomes of therapy: vancomycin-resistant enterococcal bacteremia in hematology and bone marrow transplant patients. Support Care Cancer **19:**1969–1974.
23. **Florescu I, Beuran M, Dimov R, Razbadauskas A, Bochan M, Fichev G, Dukart G, Babinchak T, Cooper CA, Ellis-Grosse EJ, Dartois N, Gandjini H.** 2008. Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococci: a phase 3, multicentre, double-blind, randomized study. J. Antimicrob. Chemother. **62**(Suppl. 1):i17–i28.
24. **Carpenter CF, Chambers HF.** 2004. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. Clin. Infect. Dis. **38:**994–1000.
25. **Arias CA, Contreras GA, Murray BE.** 2010. Management of multidrug-resistant enterococcal infections. Clin. Microbiol. Infect. **16:**555–562.
26. **McKinnell JA, Patel M, Shirley RM, Kunz DF, Moser SA, Baddley JW.** 2011. Observational study of the epidemiology and outcomes of vancomycin-resistant *Enterococcus* bacteraemia treated with newer antimicrobial agents. Epidemiol. Infect. **139:**1342–1350.
27. **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.
28. **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.
29. **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.
30. **Bio LL, Perez ME, MacDougall C, Gallagher JC.** 2011. Comparison of linezolid and daptomycin in the treatment of vancomycin-resistant enterococcal bacteremia. Infect. Dis. Clin. Pract. **19:**343–347.
31. **Eliopoulos GM, Willey S, Reiszner E, Spitzer PG, Caputo G, Moellering RC, Jr.** 1986. In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic. Antimicrob. Agents Chemother. **30:**532–535.
32. **Sader HS, Streit JM, Fritsche TR, Jones RN.** 2004. Antimicrobial activity of daptomycin against multidrug-resistant Gram-positive strains collected worldwide. Diagn. Microbiol. Infect. Dis. **50:**201–204.
33. **Moise PA, Hershberger E, Amodio-Groton MI, Lamp KC.** 2009. Safety and clinical outcomes when utilizing high-dose (≥8 mg/kg) daptomycin therapy. Ann. Pharmacother. **43:**1211–1219.
34. **Kullar R, Davis SL, Levine DP, Zhao JJ, Crank CW, Segreti J, Sakoulas G, Cosgrove SE, Rybak MJ.** 2011. High-dose daptomycin for treatment of complicated gram-positive infections: a large, multicenter, retrospective study. Pharmacotherapy **31:**527–536.
35. **Moellering RC.** 2003. Linezolid: the first oxazolidinone antimicrobial. Ann. Intern. Med. **138:**135–142.
36. **Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ.** 2003. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. Clin. Infect. Dis. **36:**159–168.
37. **Dubrovskaya Y, Kubin C, Furuya E.** 2008. Daptomycin compared to linezolid for primary treatment of vancomycin-resistant enterococcal bacteremia (VREB), abstr K-3443, p539. Abstr. 48th Intersci. Conf. Antimcrob. Agents Chemother. Washington, DC.
38. **Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB.** 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA **283:**2008–2012.
39. **Bickel PJ, Hammel EA, O'Connell JW.** 1975. Sex bias in graduate admissions: data from Berkeley. Science **187:**398–404.
40. **Pearl J.** 2000. Causality: models, reasoning, and inference. Cambridge University Press, Cambridge, United Kingdom.
41. **Furuya EY, Kubin C, Yin M, et al.** 2005. Daptomycin experience and comparison with linezolid for the treatment of vancomycin-resistant enterococcal bacteremia, abstr K-2116, p379. Abstr. 45th Intersci. Conf. Antimcrob. Agents Chemother. Washington, DC.
42. **Lu CL, Chuang YC, Chang HC, Chen YC, Wang JT, Chang SC.** 2012. Microbiological and clinical characteristics of vancomycin-resistant *Enterococcus faecium* bacteraemia in Taiwan: implication of sequence type for prognosis. J. Antimicrob. Chemother. **67:**2243–2249.
43. **Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, Sobel JD, Pappas PG, Kullberg BJ, Mycoses Study Group.** 2012. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin. Infect. Dis. **54:**1110–1122.
44. **Sakoulas G, Bayer AS, Pogliano J, Tsuji BT, Yang SJ, Mishra NN, Nizet V, Yeaman MR, Moise PA.** 2012. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. Antimicrob. Agents Chemother. **56:** 838–844.
45. **Moise PA, Lamp KC, DePestel DD, Yoon MJ, Zervos MJ.** 2012. Daptomycin (D) with or without concomitant beta-lactams (BL) for vancomycin-resistant enterococcus (VRE) bacteremia, abstr K-276. Abstr. 52nd Intersci. Conf. Antimcrob. Agents Chemother. San Francisco, CA.
46. **Talbot GH, Powers JH, Fleming TR, Siuciak JA, Bradley J, Boucher H.** 2012. Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin. Infect. Dis. **55:** 1114–1121.

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Systematic Review and Meta-Analysis of Linezolid versus Daptomycin for Treatment of Vancomycin-Resistant Enterococcal Bacteremia

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Limited therapeutic options exist for the treatment of vancomycin-resistant *Enterococcus* (VRE) bacteremia; the most commonly used are daptomycin and linezolid. We attempted a systematic review and meta-analysis of the comparative efficacy of those two agents. Studies comparing daptomycin to linezolid treatment for VRE bacteremia, published until August 2012, were identified from the MEDLINE, EMBASE, CENTRAL, ISI Web of Science, and SCOPUS databases. All comparative studies on patients older than 18 years of age that provided mortality data were considered eligible for this systematic review and meta-analysis. The primary outcome of the meta-analysis was 30-day all-cause mortality. Ten retrospective studies including 967 patients were identified. Patients treated with daptomycin had significantly higher 30-day all-cause mortality (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.08 to 2.40) and infection-related mortality (OR, 3.61; 95% CI, 1.42 to 9.20) rates than patients treated with linezolid. When data from all 10 studies were combined, overall mortality was also significantly increased among patients treated with daptomycin (OR, 1.41; 95% CI, 1.06 to 1.89). These findings were confirmed when odds ratios adjusted for potential confounders were pooled. Relapse rates among patients treated with daptomycin were also higher (OR, 2.51; 95% CI, 0.94 to 6.72), although this difference did not reach statistical significance. Adverse event rates were not significantly different between the two groups. Notwithstanding the absence of randomized prospective data, available evidence suggests that mortality rates may be higher with daptomycin than with linezolid among patients treated for VRE bacteremia.

Enterococci are the third most common cause of health care-associated bloodstream infections (BSIs) (1). Vancomycin is the first-line treatment of BSIs caused by ampicillin-resistant enterococci; however vancomycin-resistant enterococci (VRE) nowadays account for approximately one-third of the enterococcal health care-associated infections in the United States (2) and for more than 20% of such infections in some European countries (3). Mortality rates in patients with VRE BSIs range between 20 and 46% (4–6). Patients with BSI due to VRE are 2.5 times more likely to die than patients with BSI due to vancomycin-susceptible strains (7).

Treatment of VRE BSIs is particularly challenging. Strains causing such infections are usually resistant to ampicillin (8), and therapeutic options include linezolid, daptomycin, quinupristin-dalfopristin, tigecycline, teicoplanin, and telavancin (for which limited clinical data are available). Teicoplanin is not available in the United States and can only be used for some VRE infections (i.e., strains with the VanB [vancomycin-resistant, teicoplanin-susceptible] phenotype and the rare species *Enterococcus gallinarum* and *E. casseliflavus*). Tigecycline does not achieve high serum concentrations and has not been approved for treatment of bacteremias (9). Use of quinupristin-dalfopristin (effective only against *E. faecium*) is limited by the need of central venous access for administration, frequent side effects, and drug interactions (10).

Clinical experience and data for the treatment of VRE BSIs are available mainly for linezolid and daptomycin. Linezolid has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of vancomycin-resistant *E. faecium* infections, including those with concurrent bacteremia. Although daptomycin is not FDA approved for the treatment of VRE bacteremia, its rapid bactericidal activity (11, 12) offers an off-label alternative (13, 14). According to the relevant clinical practice guidelines of the Infectious Diseases Society of America, linezolid or daptomycin is recommended for the treatment of catheter-related BSIs caused by ampicillin- and vancomycin-resistant enterococci (15). Limited data exist on the comparative efficacy of daptomycin versus linezolid for enterococcal bacteremias (5, 6). Herein we summarize the available evidence and provide estimates of the clinical effectiveness of linezolid versus daptomycin for the treatment of VRE bacteremia by using meta-analytic methodology.

MATERIALS AND METHODS

Search strategy. A computerized literature search in the MEDLINE, EMBASE, CENTRAL, ISI Web of Science, and SCOPUS electronic databases covering the period until 31 August 2012 was performed independently by two individuals. The strategy employed for this study is presented in detail in the supplemental material.

Selection of studies. In order for the studies to be eligible for this systematic review, the following inclusion criteria were established prior to literature search: (i) studies should compare the outcomes of treatment between daptomycin and linezolid for VRE bacteremia in two groups of patients, (ii) patients should be older than 18 years, and (iii) the study should provide data on patient mortality outcomes.

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All studies identified to address the research question were initially considered for the present systematic review, regardless of the direction of study (retrospective or prospective) and the sample size. Case reports and case series of patients treated with either one of the two agents were not included.

Studies identified. The electronic search resulted in the retrieval of 2,365 publications (see Fig. S1 in the supplemental material). Their titles were screened to exclude irrelevant studies, resulting in 46 potentially eligible studies. A search of meeting abstracts resulted in the retrieval of eight additional studies. Of the total of 54 studies, 39 were excluded after examination of their abstracts (8 retrospective, noncomparative studies, 26 reviews and opinion papers, and 5 irrelevant studies), while 4 further studies published in meeting proceedings were excluded because they provided data already included in the identified published full texts (overlapping publications) (16–19). Eventually, 11 studies were considered for further evaluation. One study was excluded at this stage because daptomycin was not included in the comparator agents (20).

The full reference lists of the studies whose full text was examined were hand searched, which did not result in the identification of any additional studies, nor did a search of the clinical trial registries. Eventually, 10 studies comparing the efficacy of daptomycin and linezolid for the treatment of VRE bacteremia were included in this systematic review and meta-analysis (5, 6, 21–28).

Data extraction. The methodology that was followed for extracting the data is described in the supplemental material.

Outcomes. The primary outcome examined in the meta-analysis was mortality, expressed as 30-day all-cause mortality (defined as death from any reason within 30 days from the first culture positive for VRE). Infection-related mortality (defined as death attributed to VRE bacteremia) and in-hospital mortality (defined as death from any reason during hospital stay) were also evaluated. Since mortality endpoints were different across studies, a composite outcome—defined as overall mortality—was also calculated by including any relevant comparison on mortality rates between daptomycin and linezolid, irrespective of the definition used (i.e., all-cause, infection-related, in-hospital, 30-day, etc.). When some data on the outcomes of interest were not provided in the full-text papers or abstracts, the authors were contacted for further information.

Secondary outcome measures included (i) clinical cure (defined as a resolution of signs and/or symptoms of infection after treatment for VRE was discontinued), (ii) microbiological cure (with the last blood culture drawn after initiation of VRE treatment being negative), (iii) recurrence of VRE bacteremia (with a posttreatment blood culture positive for VRE following at least one negative blood culture), and (iv) adverse events (defined as the development of an adverse event proven or suspected to be related to the agent used for VRE treatment or to the route of administration).

Quantitative data synthesis. Information on quantitative data synthesis is presented in detail in the supplemental material.

RESULTS

Systematic review. The 10 studies identified as fulfilling the inclusion criteria for the systematic review included 967 patients in total. The characteristics of those studies are listed in Tables S2 to S4 in the supplemental material.

All studies were published between 2005 and 2012 and were of a retrospective cohort nature. Two were multicenter studies (22, 28), seven reported the experience of single centers, and in one case this information was not provided (27). The primary outcome measure was microbiological cure in two studies (21, 28), 30-day all-cause mortality in one study (5), and clinical and microbiological cure in one study (6), while in five studies the primary outcome among those examined was not stated.

The sample sizes of the included studies ranged from 31 to 201 patients (median, 82 patients). With two exceptions (26, 27), the studies included mixed populations, with various percentages of immunocompromised and nonimmunocompromised patients (see Table S2 in the supplemental material).

Definitions of VRE BSIs differed slightly across studies. The Centers for Disease Control and Prevention (CDC) definition for enterococcal bacteremia was used in four studies (5, 21, 26, 28). Two or more positive blood cultures or one positive blood culture with an identifiable source in a clinical scenario consistent with bacteremia defined VRE bacteremia in one study (22). The presence of one or more blood cultures positive for VRE (without further clarifications) was used in three studies (6, 23, 25). In the remaining two studies, an explicit definition of VRE BSI was not provided (24, 27).

Statistically significant differences in potential confounders between groups of patients treated with daptomycin or linezolid are listed in Table S3 in the supplemental material. Adjustments for potential confounders were performed by the authors in six studies, using multivariable logistic regression analysis (5, 21–23, 25, 28).

The median daily daptomycin dose was 6 mg/kg of body weight in six studies (6, 21–23, 27, 28), 5.5 mg/kg in one study (26), and not reported in three studies (5, 24, 25). The median duration of treatment ranged from 13 to 15 days in the daptomycin group and from 11 to 15 days in the linezolid group (21–23, 28). Combination with aminoglycosides was reported in two studies (22, 28). Patients simultaneously treated with more than one anti-VRE agent were excluded in two studies (6, 21) (see Table S4 in the supplemental material).

Prior vancomycin use was reported in two studies (22, 28) and was significantly different across groups in one of them (22). Four studies reported inclusion of patients with endocarditis (6, 21, 22, 28). Outcomes of these patients were reported separately from those for nonendocarditis bacteremia in one study only (28). Patients were switched from linezolid to daptomycin during treatment of bacteremia in two studies (due to failure, intolerance, or clinical preference [22] or to resistance or intolerance [25]), and one patient was switched from daptomycin to linezolid due to adverse events (26). Linezolid susceptibility was tested in three studies (6, 21, 26), and daptomycin susceptibility was tested in two studies (6, 21).

Meta-analysis. (i) Thirty-day all-cause mortality. All-cause mortality at 30 days (our prespecified primary endpoint) was significantly increased in patients treated with daptomycin compared to those treated with linezolid (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.08 to 2.40; fixed-effects model; heterogeneity $P = 0.42$) (Fig. 1a). No publication bias was detected (Egger's test $P = 0.84$). Four studies offered data for this outcome (5, 6, 23, 26).

In two studies, odds ratios were adjusted for potential confounders in multivariate logistic regression models (5, 23). When these were combined, a statistically significant increase in mortality rate was still present for patients of the daptomycin group compared to those in the linezolid group (adjusted OR, 2.56; 95% CI, 1.29 to 5.08; fixed-effects model; heterogeneity $P = 0.36$) (Fig. 1b).

(ii) Infection-related mortality. Infection-related mortality was significantly higher in patients who received daptomycin than in those who received linezolid (OR, 3.61; 95% CI, 1.42 to 9.20; fixed-effects model; heterogeneity $P = 0.49$) (Fig. 2a). Adjusted odds ratios for infection-related mortality were not available.

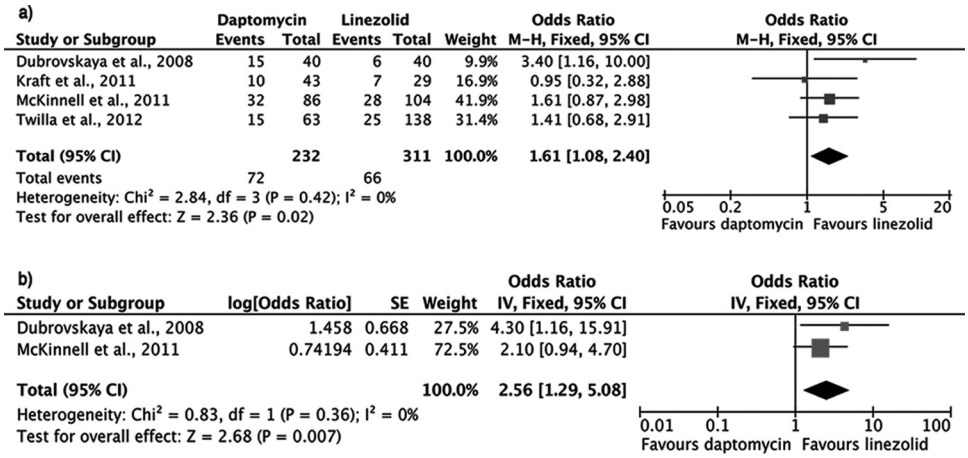

FIG 1 Forest plots (using Mantel-Haenszel [M-H] analysis) of unadjusted (a) and adjusted (b) odds ratios for 30-day all-cause mortality among patients treated with linezolid or daptomycin for VRE bacteremia. CI, confidence interval; SE, standard error; IV, Inverse variance.

(iii) In-hospital mortality. The in-hospital mortality rate was significantly higher with daptomycin than with linezolid (OR, 1.83; 95% CI, 1.05 to 3.20; fixed-effects model; heterogeneity $P = 0.69$) (Fig. 2b). Two studies estimated adjusted odds ratios for in-hospital mortality after controlling for potential confounders in multivariate logistic regression models (22, 28). When these data were combined, a higher mortality with daptomycin was observed; however, the difference did not reach statistical significance (OR, 1.65; 95% CI, 0.56 to 4.90; fixed-effects model; heterogeneity $P = 0.95$).

In the study by Crank et al., 21 patients were switched to daptomycin after linezolid failure, intolerance, or other reason as determined by the treating physicians (22). The odds ratio for mortality in this case was calculated after excluding these 21 patients, while the adjusted odds ratios provided by the authors of the study were statistically controlled for prior linezolid use.

(iv) Overall mortality. The overall mortality rate, as defined for the purposes of this meta-analysis, was significantly increased in patients treated with daptomycin compared to those treated with linezolid for VRE bacteremia (OR, 1.41; 95% CI, 1.06 to 1.89; fixed-effects model; heterogeneity $P = 0.50$). No publication bias was detected (Egger's test $P = 0.58$) (Fig. 3a).

In the study by Furuya et al., a significant proportion of patients were switched to daptomycin following linezolid failure or intolerance (25). Since this could have potentially resulted in bias, we performed a sensitivity analysis excluding this study, which did not substantially alter the findings (OR, 1.48; 95% CI, 1.09 to 2.00; fixed-effects model; heterogeneity $P = 0.54$).

Five studies provided adjusted odds ratios after controlling for potential confounders (5, 21–23, 28). When these data were pooled, overall mortality was still significantly increased in the daptomycin group compared to the linezolid group (OR, 1.99; 95% CI, 1.19 to 3.32; fixed-effects model; heterogeneity $P = 0.71$) (Fig. 3b).

(v) Clinical cure. A significant difference in clinical cure rate was not detected in patients treated with daptomycin compared to those treated with linezolid (OR, 1.04; 95% CI, 0.63 to 1.72; fixed-effects model; heterogeneity $P = 0.12$). Three studies provided data for this outcome (6, 21, 24).

(vi) Microbiological cure. Microbiological cure rates did not

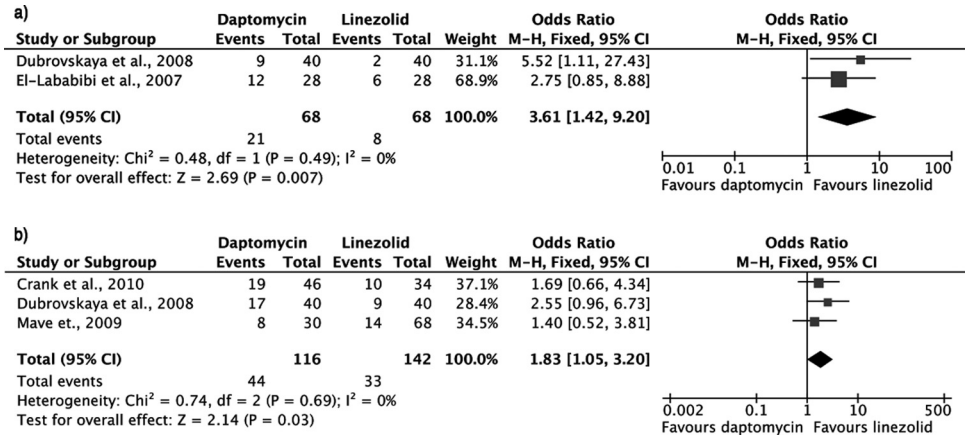

FIG 2 Forest plots (using Mantel-Haenszel [M-H] analysis) of odds ratios for infection-related mortality (a) and in-hospital mortality (b) among patients treated with linezolid or daptomycin for VRE bacteremia.

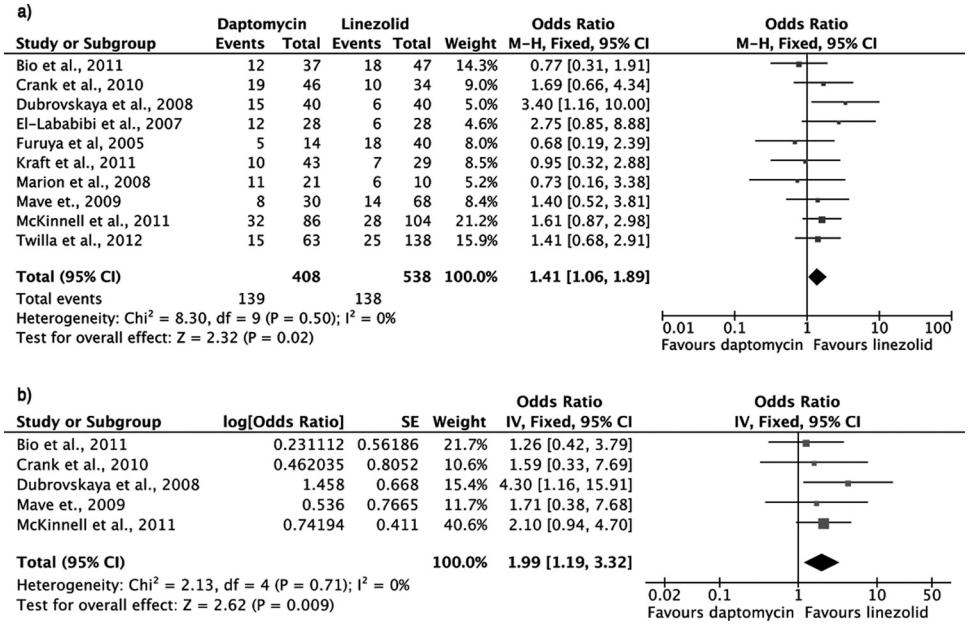

FIG 3 Forest plots (using Mantel-Haenszel [M-H] analysis) of unadjusted (a) and adjusted (b) odds ratios for overall mortality among patients treated with linezolid or daptomycin for VRE bacteremia.

differ significantly between the two groups (OR, 0.75; 95% CI, 0.41 to 1.39; fixed-effects model; heterogeneity $P = 0.76$) (Fig. 4a). Six studies offered data on this outcome (6, 21, 23, 24, 27, 28).

(vii) Recurrence of VRE bacteremia. There was a trend toward higher relapse rates among patients treated with daptomycin than among those treated with linezolid, with the difference marginally failing to reach statistical significance (OR, 2.51; 95% CI, 0.94 to 6.72; fixed-effects model; heterogeneity $P = 0.42$) (Fig. 4b). Data for this outcome were provided by four studies (6, 21, 27, 28).

(viii) Adverse events. Notwithstanding the study of Kraft et al., which reported a significant difference in increased liver function tests among patients treated with daptomycin (26), no significant differences in adverse event rates between the two groups were detected when data from individual studies were combined (see Table S5 in the supplemental material).

DISCUSSION

The present systematic review and meta-analysis summarizes the available data regarding the efficacy of linezolid versus daptomycin for the treatment of VRE bacteremia. To the best of our knowledge, this is the first study that attempts to critically appraise the existing evidence on this controversial issue. Based on the meta-analysis results, 30-day all-cause mortality was significantly higher among patients with VRE bacteremia who were treated with dap-

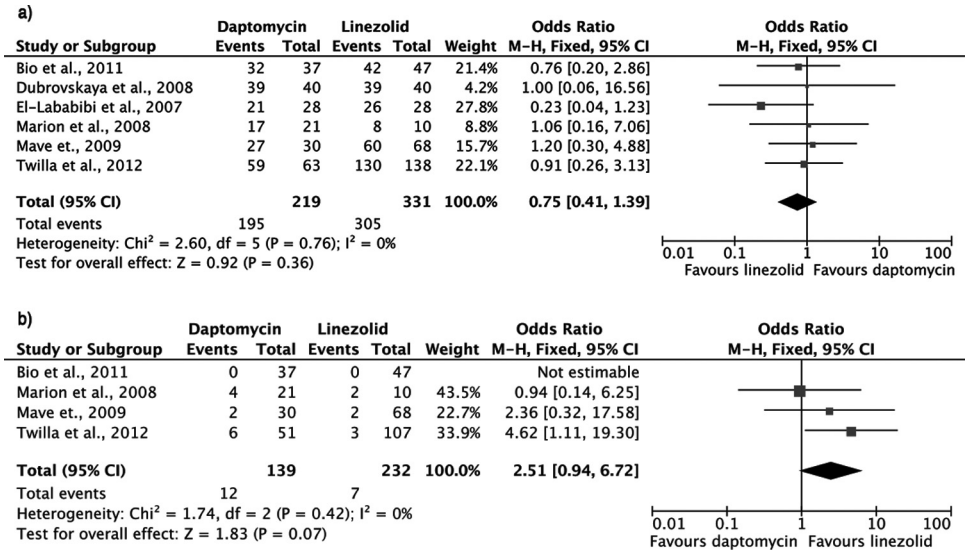

FIG 4 Forest plots (using Mantel-Haenszel [M-H] analysis) of odds ratios for microbiological cure (a) and bacteremia recurrence (b) in patients treated with daptomycin or linezolid for VRE bacteremia.

tomycin than among those treated with linezolid. Notably, the in-hospital mortality and infection-related mortality rates were also increased in the daptomycin group compared to the linezolid group. These findings were not materially altered in the sensitivity analyses (performed by pooling the adjusted odds ratios for mortality that were provided by the authors of individual studies). Administration of both drugs was relatively safe in high-risk patient cohorts, and the frequency of adverse events did not seem to differ between the two treatment options.

An important strength of meta-analysis is its inherent ability to increase the statistical power of individual studies. Notably, most of the studies included in this analysis showed a trend toward increased mortality rates among patients treated with daptomycin. With the exception, however, of one study (23), the difference from linezolid did not reach statistical significance. When the results of individual studies were combined, a significant increase in all mortality outcomes in the daptomycin group surfaced, coupled with negligible ($I^2 = 0\%$) heterogeneity across studies. We acknowledge, however, that despite the absence of statistical heterogeneity, significant clinical heterogeneity was present across the studies analyzed (i.e., in terms of patients included, other antibiotics used, doses, etc. [summarized in Tables S2 to S4 in the supplemental material]). For this reason, the results of the studies were also combined with the use of a random-effects model, and the pooled estimates for all mortality outcomes remained unaltered (data not shown). Hence, the results obtained in this meta-analysis are stable and thus seem to accurately reflect the underlying effect present in the available comparative studies.

In order to further increase the statistical power of this meta-analysis, the composite outcome of overall mortality rate was calculated. This outcome combined data on mortality from individual studies, whether this was expressed as 30-day all-cause mortality ($n = 4$) (5, 6, 23, 26), in-hospital mortality ($n = 2$) (22, 28), infection-related mortality ($n = 1$) (24), mortality at the end of therapy ($n = 1$) (25), mortality 7 days after the end of therapy ($n = 1$) (21), or overall mortality ($n = 1$) (27). The pooled overall mortality rate confirmed the findings of primary analysis.

Certain limitations apply for the interpretation of our results. All available studies were retrospective and observational. The possibility of significant confounders therefore exists (e.g., selection bias, with patients with worse prognoses being treated with daptomycin, patients able to swallow being treated with linezolid, etc.). A proportion of patients treated with either agent were later changed to the other (usually due to failure), had previously received another antibiotic (typically vancomycin), or had additional organisms recovered in blood cultures. Characteristics such as the presence of endocarditis (6, 21, 22, 28), source of any secondary bacteremias (21, 22) (including the rare possibility of enterococcal pneumonias, where daptomycin would not be indicated), treating physicians and ID consultations (5), daptomycin dosing (6, 21–23, 26–28), and combination therapies (22, 28) were not available for all patients. Although such biases cannot be eliminated outside the context of a randomized prospective trial, we note that results from adjustment that took into account known confounders (listed in Table S3 in the supplemental material) were all in agreement with those of the primary analysis. We also note that pooling such patients (i.e., patients with and without endocarditis, with and without additional therapies, etc.) in itself risks introducing bias. Even so, consistent results in favor of linezolid were obtained when authors of individual studies adjusted for known confounders (5, 21–23, 28). Notably, similar characteristics between the two patient groups were recorded in most studies; in fact, factors associated with unfavorable prognosis were overrepresented among the linezolid patient group in some studies (i.e., patients who were older [5, 6, 28], in the intensive care unit [ICU] [21], or had higher APACHE scores [28]). On the other hand, whether daptomycin or linezolid is advantageous in specific patient populations (e.g., hemodialysis, transplant recipients, etc.) could not be evaluated in the present study due to the limited number of data available.

A potential explanation for the observed inferior outcomes for patients treated for VRE bacteremia with a bactericidal agent (daptomycin) compared to those treated with a bacteriostatic (linezolid) should perhaps be sought in the context of recent reports on daptomycin failures during treatment of enterococcal infections and emergence of resistance, especially among VRE strains (29–31). In regards to this, we note the higher (although marginally failing statistical significance tests) relapse rates of VRE bacteremia following daptomycin treatment than following linezolid treatment in our analysis (Fig. 4b). In contrast with mortality and tendency toward relapses, clinical and microbiological cure rates did not differ between the two agents. Given that neither mortality cause nor clinical/microbiological cure data were available for all studies, a definite conclusion on any relationship between those outcomes cannot be drawn with certainty.

Optimal daptomycin dosing for treatment of severe infections remains a challenge, as higher doses have been proposed (30, 32) and recently supported by *in vitro* data on VRE (33). Inferences regarding the optimal dose of daptomycin for treating VRE bacteremia could not be made from this review, since six of seven studies used a median dose of 6 mg/kg (6, 21–23, 27, 28), while one study used a median dose of 5.5 mg/kg (26). It is possible that some of the suboptimal outcomes were associated with daptomycin underdosing (i.e., <6 mg/kg). Whether even higher, off-label daptomycin doses would increase efficacy in the treatment of VRE bacteremia, without increasing toxicity, also remains to be explored. Similarly, the effect of proposed strategies of combination treatment with daptomycin and ampicillin (31) or rifampin (34) could not be assessed adequately from these data.

Based on the evidence summarized herein, daptomycin may be associated with worse outcomes in patients treated for VRE bacteremia than linezolid. Given, however, the methodologic limitations of the existing studies, a properly designed randomized controlled multicenter trial to evaluate therapeutic options for VRE bacteremia is required, although this would be a challenging task.

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E.P.B. and C.A.V. performed the computerized literature search in the MEDLINE, EMBASE, CENTRAL, ISI Web of Science, and SCOPUS electronic databases.

REFERENCES

1. **Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB.** 2004. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin. Infect. Dis. **39:**309–317. http://dx.doi.org/10.1086/421946.
2. **Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA,**

Fridkin SK. 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. http://dx.doi.org/10.1086/591861.

3. **European Centre for Disease Prevention and Control.** 2010. Antimicrobial resistance surveillance in Europe 2009. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). ECDC, Stockholm, Sweden. http://ecdc.europa.eu/en/publications/Publications/1011_SUR_annual_EARS_Net_2009.pdf.
4. **Han SH, Chin BS, Lee HS, Jeong SJ, Choi HK, Kim CO, Yong D, Choi JY, Song YG, Lee K, Kim JM.** 2009. Vancomycin-resistant enterococci bacteremia: risk factors for mortality and influence of antimicrobial therapy on clinical outcome. J. Infect. **58:**182–190. http://dx.doi.org/10.1016/j.jinf.2009.01.013.
5. **McKinnell JA, Patel M, Shirley RM, Kunz DF, Moser SA, Baddley JW.** 2011. Observational study of the epidemiology and outcomes of vancomycin-resistant Enterococcus bacteraemia treated with newer antimicrobial agents. Epidemiol. Infect. **139:**1342–1350. http://dx.doi.org/10.1017/S0950268810002475.
6. **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.
7. **DiazGranados CA, Zimmer SM, Klein M, Jernigan JA.** 2005. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. Clin. Infect. Dis. **41:**327–333. http://dx.doi.org/10.1086/430909.
8. **Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN.** 2007. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. Diagn. Microbiol. Infect. Dis. **58:**163–170. http://dx.doi.org/10.1016/j.diagmicrobio.2006.12.022.
9. **Arias CA, Contreras GA, Murray BE.** 2010. Management of multidrug-resistant enterococcal infections. Clin. Microbiol. Infect. **16:**555–562. http://dx.doi.org/10.1111/j.1469-0691.2010.03214.x.
10. **Rubinstein E, Prokocimer P, Talbot GH.** 1999. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. J. Antimicrob. Chemother. **44**(Suppl A):37–46. http://dx.doi.org/10.1093/jac/44.suppl_1.37.
11. **Akins RL, Rybak MJ.** 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. http://dx.doi.org/10.1128/AAC.45.2.454-459.2001.
12. **Jorgensen JH, Crawford SA, Kelly CC, Patterson JE.** 2003. In vitro activity of daptomycin against vancomycin-resistant enterococci of various Van types and comparison of susceptibility testing methods. Antimicrob. Agents Chemother. **47:**3760–3763. http://dx.doi.org/10.1128/AAC.47.12.3760-3763.2003.
13. **Kvirikadze N, Suseno M, Vescio T, Kaminer L, Singh K.** 2006. Daptomycin for the treatment of vancomycin resistant Enterococcus faecium bacteremia. Scand. J. Infect. Dis. **38:**290–292. http://dx.doi.org/10.1080/00365540500434687.
14. **Poutsiaka DD, Skiffington S, Miller KB, Hadley S, Snydman DR.** 2007. Daptomycin in the treatment of vancomycin-resistant Enterococcus faecium bacteremia in neutropenic patients. J. Infect. **54:**567–571. http://dx.doi.org/10.1016/j.jinf.2006.11.007.
15. **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.
16. **Crank CW, Scheetz M, Brielmaier B, Rose W, Patel G, Ritchie D, Segreti J.** 2008. Comparison of daptomycin (D) vs. linezolid (L) for vancomycin-resistant enterococcal bacteremia (VRE), abstr K-3442. Abstr. Joint 48th Intersci. Conf. Antimicrob. Agents Chemother. 46th Infect. Dis. Soc. Am. Annu. Meet.
17. **Locastro LG, Perez ME, Marino EA, Abrardo LA, Gallagher JC.** 2008. Comparison of linezolid (LZD) and daptomycin (DAP) for vancomycin-resistant Enterococcus bacteremia (VREB), abstr K-3440. Abstr. Joint 48th Intersci. Conf. Antimicrob. Agents Chemother. 46th Infect. Dis. Soc. Am. Annu. Meet.
18. **Mave V, Hasbun R, Garcia-Diaz J.** 2007. Vancomycin-resistant enterococcal bacteraemia: is daptomycin as effective as linezolid?, abstr 1090. Abstr. 45th Annu. Meet. Infect. Dis. Soc. Am.
19. **McKinnell JA, Patel M, Shirley RM, Kunz DF, Baddley JW.** 2009. Clinical outcomes with linezolid and daptomycin for the treatment of VRE bacteremia, abstr K-1603. Abstr. 49th Intersci. Conf. Antimicrob. Agents Chemother.
20. **Erlandson KM, Sun J, Iwen PC, Rupp ME.** 2008. Impact of the more-potent antibiotics quinupristin-dalfopristin and linezolid on outcome measure of patients with vancomycin-resistant Enterococcus bacteremia. Clin. Infect. Dis. **46:**30–36. http://dx.doi.org/10.1086/523588.
21. **Bio LL, Perez ME, MacDougall C, Gallagher JC.** 2011. Comparison of linezolid and daptomycin in the treatment of vancomycin-resistant enterococcal bacteremia. Infect. Dis. Clin. Pract. **19:**343–347. http://dx.doi.org/10.1097/IPC.0b013e31822b7f6e.
22. **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.
23. **Dubrovskaya Y, Kubin CJ, Furuya EY.** 2008. Daptomycin (D) compared to linezolid (L) for primary treatment of vancomycin-resistant enterococcal bacteremia (VREB), abstr K-3443. Abstr. Joint 48th Intersci. Conf. Antimicrob. Agents Chemother. 46th Infect. Dis. Soc. Am. Annu. Meet.
24. **El-Lababidi RM, Topal J, Tsukerman M.** 2007. Daptomycin and linezolid in the treatment of vancomycin-resistant enterococcal bacteremia: a retrospective analysis of treatment outcomes, abstr 1095. Abstr. 45th Annu. Meet. Infect. Dis. Soc. Am.
25. **Furuya EY, Kubin C, Yin M, Lowy FD, Della-Latta P, Hammer S.** 2005. Daptomycin experience and comparison with linezolid for the treatment of vancomycin-resistant enterococcal bacteremia, abstr K-2116. bstr. 45th Intersci. Conf. Antimicrob. Agents Chemother.
26. **Kraft S, MacKler E, Schlickman P, Welch K, Depestel DD.** 2011. Outcomes of therapy: vancomycin-resistant enterococcal bacteremia in hematology and bone marrow transplant patients. Support Care Cancer **19:**1969–1974. http://dx.doi.org/10.1007/s00520-010-1038-z.
27. **Marion C, Kennedy L, High K.** 2008. Daptomycin or linezolid in the treatment of vancomycin-resistant enterococcal bacteremia in neutropenic cancer patients, abstr L-2120. Abstr. Joint 48th Intersci. Conf. Antimicrob. Agents Chemother. 46th Infect. Dis. Soc. Am. Annu. Meet.
28. **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.
29. **Kelesidis T, Humphries R, Uslan DZ, Pegues DA.** 2011. Daptomycin nonsusceptible enterococci: an emerging challenge for clinicians. Clin. Infect. Dis. **52:**228–234. http://dx.doi.org/10.1093/cid/ciq113.
30. **King ST, Usery JB, Holloway K, Koeth L, Cleveland KO, Gelfand MS.** 2011. Successful therapy of treatment-emergent, non-clonal daptomycin-non-susceptible Enterococcus faecium infections. J. Antimicrob. Chemother. **66:**2673–2675. http://dx.doi.org/10.1093/jac/dkr343.
31. **Sakoulas G, Bayer AS, Pogliano J, Tsuji BT, Yang SJ, Mishra NN, Nizet V, Yeaman MR, Moise PA.** 2012. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant Enterococcus faecium. Antimicrob. Agents Chemother. **56:**838–844. http://dx.doi.org/10.1128/AAC.05551-11.
32. **Crompton JA, North DS, McConnell SA, Lamp KC.** 2009. Safety and efficacy of daptomycin in the treatment of osteomyelitis: results from the CORE Registry. J. Chemother. **21:**414–420. http://dx.doi.org/10.1179/joc.2009.21.4.414.
33. **Hall AD, Steed ME, Arias CA, Murray BE, Rybak MJ.** 2012. Evaluation of standard- and high-dose daptomycin versus linezolid against vancomycin-resistant Enterococcus isolates in an in vitro pharmacokinetic/pharmacodynamic model with simulated endocardial vegetations. Antimicrob. Agents Chemother. **56:**3174–3180. http://dx.doi.org/10.1128/AAC.06439-11.
34. **Steenbergen JN, Mohr JF, Thorne GM.** 2009. Effects of daptomycin in combination with other antimicrobial agents: a review of in vitro and animal model studies. J. Antimicrob. Chemother. **64:**1130–1138. http://dx.doi.org/10.1093/jac/dkp346.