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EDITORIAL COMMENTARY

Linezolid vs Daptomycin for Vancomycin-Resistant Enterococci: The Evidence Gap Between Trials and Clinical Experience

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Bloodstream infections due to vancomycin-resistant enterococcal species (VRE-BSI) can be a lethal complication for hospitalized patients. VRE-BSI principally affects vulnerable patient populations, including complex postsurgical and internal medicine patients with multiple comorbid conditions [1–6]. VRE-BSI has particularly high attributable mortality in hematopoietic stem cell transplant recipients, liver transplant recipients, oncology patients, and other critically ill hospitalized populations [5–13].

Despite the high human and economic burden of VRE-BSI, the optimal treatment for these infections has not been established, and due to the fact that most enterococcal isolates (ie, *E. faecium*) are multidrug-resistant, clinicians are often faced with no reliable therapeutic options in critically ill patients. Linezolid is the only drug specifically approved by the Food and Drug Administration (FDA) for the treatment of VRE-BSI. However, studies leading to approval were based on limited data in an era where even fewer treatment options were available [6, 7]. Two phase-III clinical trials for VRE-BSI were started but were subsequently aborted due to enrollment difficulties [14, 15]. Additionally, there have been concerns that linezolid may not be optimal in deep-seated VRE infections. Linezolid is a bacteriostatic agent, and its activity may not be ideal for patients with severe VRE infections including those with infective endocarditis and other endovascular infections. Furthermore, linezolid toxicity when administered for prolonged courses may limit its use in VRE endocarditis.

Due to the above issues and despite lacking FDA approval for VRE infections, daptomycin (DAP, a lipopeptide antibiotic with in vitro bactericidal activity against VRE) has become a first-line agent to treat severe VRE infections. Although robust clinical evidence for the use of daptomycin for this indication is lacking, its in vitro profile and perceived clinical success [16] has made DAP attractive for clinicians. However, the use of DAP for these infections have several caveats including, (*i*) emergence of resistance during therapy, (*ii*) the presence of mutations associated with DAP-resistance in isolates that are currently reported as DAP "susceptible" (minimum inhibitory concentrations [MICs] 3–4 μg/mL, breakpoint 4 μg/mL) that may jeopardize DAP clinical utility as monotherapy, and (*iii*) the optimal DAP dosing for VRE infections has not been established with some in vitro data suggesting that doses of 10–12 mg/kg should be used to prevent development of resistance [17], a notion that is also supported by some clinical data indicating better outcomes with higher doses [18, 19].

There have been 3 independent systematic reviews of the literature with meta-analysis that sought to compare DAP or linezolid for treatment of VRE-BSI [20–22]. Although the studies differed in some regards, all 3 meta-analysis suggested a survival benefit of linezolid over DAP. What was perhaps more impressive than the meta-analysis results was the fact that all 3 investigations found significant methodological limitations to the underlying literature. The limitations of prior studies included variable case definitions, limited sample size, heterogeneous patient

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populations, wide variation in outcome measures, insufficient DAP dosing, and documented but unadjusted treatment selection bias. The methodology of previous studies of VRE-BSI has not been robust and despite rigorous analysis of the literature, the data are not compelling to make sound therapeutic conclusions regarding the best available therapy for VRE-BSI.

Due to the limitations of available studies, the current manuscript by Britt et al represents a welcome contribution to the literature on VRE-BSI and a step forward in the quality of study design. The authors were able to harness the infrastructure of the Veterans Affairs (VA) electronic medical record to generate a multicenter national cohort investigation of the treatment of VRE-BSI. The authors were careful to choose patients only treated with DAP or linezolid, not those who received sequential treatment. Unlike other investigations, patients were treated with higher doses of DAP (6 mg/kg), although probably not optimal DAP doses for VRE [17–19]. The authors supplemented electronic data extraction with detailed chart review, including identification of negative culture results, source of infection, and source control. The authors *a priori* defined outcomes measures that have "real-world" clinical relevance. The nuts and bolts of the study were sound, and the study was well designed.

The principle conclusion of the Britt et al manuscript is that linezolid was associated with higher microbiologic failure rates, higher mortality, and more treatment failure for VRE-BSI. The finding that DAP was better than linezolid in this cohort is made even more remarkable by the fact that most patients were relatively underdosed (6 mg/kg) with DAP. As mentioned above, higher doses of DAP (>8 mg/kg or greater) are thought to improve clinical outcomes from VRE-BSI [17–19]. The relatively low dosing of DAP biased the study toward not showing a difference between agents, yet the results show a clear treatment effect of daptomycin over linezolid.

A key observation from the investigation by Britt et al is that the there were statistically significant differences between patients treated with linezolid and patients treated with DAP (Table 1). The cohort of patients treated with linezolid may actually have been "sicker" than patients treated with DAP. The linezolid cohort had more patients in intensive care (84% vs 71%, $P < .001$), higher median APACHE II score (16 vs 14, $P = .005$), and more mechanical ventilation (22% vs 11%, $P < .001$). Clinicians accustomed to reviewing clinical trials are quick to criticize nonrandomized observational studies when differences between treatment cohorts occur. However, the current study provides an example for how modern modeling techniques can adjust for observed differences between cohorts. In the unadjusted analysis presented in Table 3, linezolid was associated with treatment failure (risk ratio 1.37, $P < .001$). However, other predictor variables, including intensive care unit (ICU) admission (more common with linezolid, $P < .001$), severe liver disease (more common with DAP, $P < .010$), and median APACHE II (higher with linezolid, $P = .005$) were also associated with failure. After adjusting for the differences in the individual predictor variables, the effect size of linezolid treatment diminished (risk ratio 1.15), but linezolid did remain independently associated with treatment failure ($P = .026$).

With the failure of 2 VRE-BSI clinical trials to enroll an adequate number of subjects, and the low likelihood of having a "gold-standard" prospective randomized clinical trial, does a single well-designed observational study reporting on the largest published experience with VRE-BSI finally define the optimal therapy for VRE-BSI? We would argue that, much like clinical trials, other multisite and well-designed observational studies should be conducted to more adequately answer the question [23]. In addition to some of the limitations mentioned above, the current study is limited by being nearly all male, based only in VA medical centers, and the cohort contained relatively few transplant patients. Moreover, over 90% of subjects achieved microbiologic clearance, suggesting that this population may not have been as sick as other published cohorts. Indeed, over one-third of the VRE-BSI was line related, and line removal may have played a part in the microbial eradication. Although likely not generalizable for all medical centers, the results of the current manuscript should be reassuring for those who routinely use DAP for VRE-BSI.

The report by Britt et al makes other observations that are relevant to clinical care of patients. First, the data confirm prior observations that VRE-BSI is a serious complication of hospitalization. Treatment failure in this population was over 60%, and the cohort had nearly 10% mortality at 7 days. Second, the data from the current study further support that effective antibiotic therapy and shorter duration of bacteremia are associated with lower mortality in patients with VRE-BSI [5, 8, 13, 24, 25]. Lastly, as it has been shown repeatedly in infectious disease research, time to effective treatment was highly associated with treatment success (68 hours vs 86 hours, $P < .001$) (Supplementary Table 2). The importance of time to effective treatment indicates that clinicians should maintain vigilance for patients at risk for VRE-BSI and consider early empiric therapy with activity against VRE-BSI to improve outcomes.

Recent clinical and laboratory investigations suggest that DAP nonsusceptible enterococci may be more prone to be killed by the combination of DAP and β-lactams, despite the fact that they exhibit high MICs to ampicillin. This synergistic effect has been observed with ampicillin, ceftaroline, and most recently with ertapenem. Although the mechanistic basis for such synergism are obscure, the addition of β-lactam may improve the avidity of DAP (and, possibly, other cationic antimicrobial peptides produced by the innate immune system) for its cell membrane target by altering the surface

charge [26]. A caveat is that the effect may be dependent on the genetic background of the infecting strain and the "pathway" for DAP resistance [27]. In the analysis by Britt et al, concomitant treatment with β-lactam antibiotics did not affect clinical outcomes. In a recent analysis of a multicenter registry study of DAP (The Cubicin Outcomes Registry and Experience), concomitant β-lactam therapy did not seem to affect outcomes in the overall cohort but may have improved outcomes when the DAP MICs were 3–4 μg/mL [28]. Unfortunately, relatively few patients in the current investigation had measurement of DAP MIC. The impact of concomitant β-lactam therapy on outcomes of VRE-BSI, particularly in salvage therapy or when the DAP MIC is 3–4 μg/mL, remains an open question that will ultimately require further investigation.

What further distinguishes the investigation by Britt et al is the rigorous validation of electronic data and the use of modern statistical methods to draw conclusions from "real-world" nonrandomized observational research. Although a review of the modern methods of causal inference is beyond the scope of this manuscript [29–31], the use of Cox proportional hazard modeling and propensity score analysis to adjust for treatment selection and confounding should be seen as a strong contribution from this manuscript. Despite the good methodological approach, the best therapeutic strategy to treat VRE BSI remains to be established. Although prospective, randomized trials are urgently needed, there are no further plans to initiate phase II or phase III clinical trials for VRE-BSI to our knowledge. Without randomized controlled trials to guide therapy, rigorously conducted retrospective studies can provide some guidance for treatment decisions that must be made today.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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MAJOR ARTICLE

Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin-Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients

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(See the Editorial Commentary by McKinnell and Arias on pages 879–82.)

Background. Vancomycin-resistant *Enterococcus* bloodstream infections (VRE-BSIs) are becoming increasingly common. Linezolid and daptomycin are the primary treatment options for VRE-BSI, but optimal treatment is unclear.

Methods. This was a national retrospective cohort study comparing linezolid and daptomycin for the treatment of VRE-BSI among Veterans Affairs Medical Center patients admitted during 2004–2013. The primary outcome was treatment failure, defined as a composite of (1) 30-day all-cause mortality; (2) microbiologic failure; and (3) 60-day VRE-BSI recurrence. Poisson regression was conducted to determine if antimicrobial treatment was independently associated with clinical outcomes.

Results. A total of 644 patients were included (linezolid, n = 319; daptomycin, n = 325). Overall, treatment failure was 60.9% (n = 392/644), and 30-day all-cause mortality was 38.2% (n = 246/644). Linezolid was associated with a significantly higher risk of treatment failure compared with daptomycin (risk ratio [RR], 1.37; 95% confidence interval [CI], 1.13–1.67; $P = .001$). After adjusting for confounding factors in Poisson regression, the relationship between linezolid use and treatment failure persisted (adjusted RR, 1.15; 95% CI, 1.02–1.30; $P = .026$). Linezolid was also associated with higher 30-day mortality (42.9% vs 33.5%; RR, 1.17; 95% CI, 1.04–1.32; $P = .014$) and microbiologic failure rates (RR, 1.10; 95% CI, 1.02–1.18; $P = .011$). No difference in 60-day VRE-BSI recurrence was observed between treatment groups.

Conclusions. Treatment with linezolid for VRE-BSI resulted in significantly higher treatment failure in comparison to daptomycin. Linezolid treatment was also associated with greater 30-day all-cause mortality and microbiologic failure in this cohort.

Keywords. bloodstream infection; *Enterococcus*; vancomycin-resistant *Enterococcus*; daptomycin; linezolid.

Vancomycin-resistant *Enterococcus* (VRE) is a significant healthcare-associated pathogen with increasing impact in recent years [1–4]. As many as 28% of all enterococcal bloodstream isolates are now resistant to vancomycin, including a majority of *Enterococcus faecium* strains [1]. Multiple studies have shown vancomycin resistance to be independently associated with mortality in VRE bloodstream infections (VRE-BSIs), with mortality rates 2–3 times that of vancomycin-susceptible infections [5–7]. Among critically ill and neutropenic patients with VRE-BSI, mortality may exceed 60% [6].

Despite the prevalence and severity of these infections, optimal treatment for VRE-BSI remains unclear.

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Most VRE strains are resistant to ampicillin, and current recommendations suggest linezolid or daptomycin as first-line treatment options [8, 9]. Linezolid is US Food and Drug Administration (FDA) approved for the treatment of VRE infections, including bacteremia [10]. Despite its efficacy, concerns for myelosuppression and serotonergic toxicity limit linezolid use in patients with underlying hematologic disturbances or those using concomitant serotonergic agents [10]. The bacteriostatic activity of linezolid may also limit its effectiveness in patients with endocarditis or immunosuppression [6, 11]. In these cases, an agent such as daptomycin, which exhibits concentration-dependent bactericidal activity against VRE, may be an attractive alternative [6, 12–14]. Daptomycin is recommended at a dose of 6 mg/kg/day for gram-positive BSIs, but in vitro and clinical data suggest that outcomes may be improved with higher doses [15–18]. Although daptomycin lacks an FDA indication for VRE-BSI, it is commonly used in this setting in clinical practice [19].

Multiple clinical studies have compared daptomycin and linezolid for the treatment of VRE-BSI [20–23]. A recent meta-analysis pooled data from these investigations and noted an apparent superiority of linezolid over daptomycin in overall mortality [24]. However, the heterogeneity among inclusion and exclusion criteria and outcome definitions in the pooled studies make it difficult to properly adjust for confounding factors. Nearly all the included studies noted a trend toward daptomycin treatment among patients with neutropenia, thrombocytopenia, and endocarditis [24]. Another meta-analysis noted similar treatment selection bias [25]. Previous studies comparing the 2 agents have failed to find a difference in outcomes due to inadequate statistical power [20–22]. Due to the high mortality associated with these infections, optimal treatment is essential. Therefore, the objective of this study was to compare the safety and effectiveness of linezolid vs daptomycin for treatment of VRE-BSI in a population not vulnerable to some of the limitations of previous studies.

METHODS

Study Population

This was a national retrospective cohort study of hospitalized patients admitted to any Veterans Affairs Medical Center (VAMC) between 1 January 2004 and 1 January 2013. All adult patients with at least 1 blood culture positive for VRE were included. Exclusion criteria were (1) treatment with another anti-VRE agent; (2) treatment with linezolid and daptomycin combination therapy (including sequential treatment); and (3) treatment with daptomycin or linezolid for <48 hours. In recurrent VRE-BSI, only the first case encountered in the study period was analyzed. This study was approved by the Kansas City VAMC institutional review board.

Data Sources

National clinical databases comprised of inpatient, outpatient, and administrative data from all VAMCs were queried to identify patients meeting study criteria. Data were abstracted from these databases and included patient demographics, laboratory and microbiologic data, vital signs, antimicrobial treatment data, comorbidities, admissions records, and dates of death. Additionally, retrospective review of the electronic medical record was conducted to collect data that were not available in these databases at the time of this study, including negative culture results, VRE-BSI source, and source control as documented by a treating physician. Susceptibilities to antimicrobial agents were determined during routine clinical care.

Outcome Measures

The primary outcome was treatment failure, defined as a composite of (1) 30-day all-cause mortality; (2) microbiologic failure (lack of microbiologic clearance among those with at least 1 follow-up blood culture); and (3) recurrence of VRE-BSI within 60 days of therapy completion. Secondary outcomes were 30-day all-cause mortality, early (7-day) mortality, hospital length of stay (LOS), and duration of bacteremia. The starting time for 30-day and 7-day mortality determinations was designated as the time of first positive VRE blood culture. Hospital LOS was defined as the number of days from the beginning of linezolid or daptomycin treatment until discharge. Duration of bacteremia was defined as the number of days between the first positive VRE blood culture and the first negative blood culture.

Adverse Events

Platelet and creatine phosphokinase (CPK) data were collected for each patient at the beginning of treatment until 3 days after the end of therapy, when available. CPK elevation was determined according to previously defined criteria [26]. Thrombocytopenia was defined as platelets <50 000 cells/μL.

Statistical Analysis

Baseline categorical variables were compared by χ^2 or 2-tailed Fisher exact test, when appropriate. Continuous variables were compared by *t* test or Mann–Whitney *U* test. Variables that were associated with treatment group or treatment failure ($P < .2$) were manually entered into a backward stepwise Poisson regression model with robust variance estimates. Variables that confounded the relationship between treatment and the primary outcome, resulting in a ≥10% change in the associated risk ratio, were retained in the final multivariable model. Time-to-event analyses were conducted for 30-day all-cause mortality and microbiologic failure using the Kaplan–Meier method, with differences in survival distributions for treatment groups compared using the log-rank test. Additionally, Cox proportional hazards models were fitted with covariates selected using a

backward stepwise approach. For time-dependent analyses, cases that did not experience the outcome of interest were right-censored at the end of the treatment period to control for potential differences in duration of therapy. Analyses were conducted to compare 30-day mortality stratified for VRE-BSI species (*E. faecium* vs *Enterococcus faecalis*) and source of infection (line vs nonline) using the Mantel–Haenszel procedure. An analysis of the effect of concomitant treatment with at least 1 dose of a β-lactam or aminoglycoside agent was conducted among daptomycin-treated subjects. A sensitivity analysis excluding cases in which the causative VRE species was not defined in the final microbiology report was conducted. Propensity score–matched analyses were also performed (Supplementary Appendix). Proportions of adverse events were compared by logistic regression. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina), with a 2-tailed *P* value <.05 considered statistically significant.

RESULTS

A total of 1109 cases of VRE-BSI met inclusion criteria during the study period. Of those cases, patients were excluded due to treatment with another anti-VRE agent (n = 25), treatment with both linezolid and daptomycin (n = 140), treatment <48 hours (n = 119), and recurrent infection (n = 181). There were 644 patients included in the final analysis, with 319 (49.5%) treated with linezolid and 325 (50.5%) treated with daptomycin. These individuals were treated at 47 distinct VAMCs across 29 states and Puerto Rico. All isolates were resistant to ampicillin. Among those treated with linezolid, susceptibility data was reported for 141 (44.2%) of VRE isolates, all of which were susceptible. Daptomycin susceptibility testing was not routinely reported and was only available in 33 (10.1%) cases, all of which were daptomycin susceptible (1 μg/mL, 7/33 [21.2%]; 2 μg/mL, 15/33 [45.5%]; 4 μg/mL, 11/33 [33.3%]).

The median daptomycin dose was 5.93 mg/kg (interquartile range [IQR], 5.33–6.10 mg/kg). Nearly all (99.4%) patients treated with linezolid were given 600-mg doses twice daily. Polymicrobial bacteremia occurred in 7.6% of cases overall, and the microbiology of these infections are reported in Supplementary Table 1. Baseline characteristics were compared according to treatment group in Table 1. As can be interpreted, there were many significant differences between linezolid- and daptomycin-treated subjects with regard to these characteristics.

Overall, treatment failure was 60.9%, 30-day all-cause mortality was 38.2%, 7-day mortality was 9.9%, median hospital LOS was 13 days (IQR, 6–25 days), and median duration of bacteremia was 3 days (IQR, 2–6 days). The association between VRE-BSI treatment and clinical outcomes is displayed in Table 2. Factors associated with treatment failure are also reported (Supplementary Table 2). In univariable analysis, treatment failure was significantly higher in the linezolid-treated group compared with the daptomycin-treated group (67.1% vs 54.8%; risk ratio [RR], 1.37; 95% confidence interval [CI], 1.13–1.67; *P* = .001). This association was driven primarily by differences between treatment groups with regard to 30-day all-cause mortality (42.9% vs 33.5%; RR, 1.17; 95% CI, 1.04–1.32; *P* = .014) and microbiologic failure (14.6% vs 6.4%; RR, 1.10; 95% CI, 1.02–1.18; *P* = .011). Treatment with linezolid also resulted in a significantly higher frequency of early mortality (12.9% vs 7.1%; RR, 1.07; 95% CI, 1.01–1.12; *P* = .016). No difference in median hospital LOS between treatment groups was observed (14 days vs 12 days; *P* = .228). Median duration of bacteremia was significantly higher among patients treated with linezolid vs daptomycin (4 days vs 3 days; *P* = .033). Excluding cases in which the causative VRE species was not defined, treatment failure remained higher among those treated with linezolid (67.0% [n = 201/300] vs 56.9% [n = 164/288]; *P* = .012).

Variables that were selected in the backward stepwise Poisson regression model for treatment failure included linezolid treatment, intensive care unit admission, severe liver disease, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The relationship between increased failure among those treated with linezolid remained after adjusting for these factors in Poisson regression (adjusted RR, 1.15; 95% CI, 1.02–1.30; *P* = .026; Table 3). In this model, every 1-unit increase in APACHE II score was associated with a 2.5% greater risk of treatment failure. All other variables, including time to VRE-BSI, time to treatment, and solid organ transplant did not confound the relationship between treatment group and composite treatment failure and therefore were not retained in the final parsimonious model.

Kaplan–Meier curves for 30-day all-cause mortality and microbiologic failure are depicted in Figure 1. Compared to linezolid, daptomycin treatment demonstrated significantly improved survival (log-rank *P* = .021) and microbiologic clearance (log-rank *P* < .001). Unadjusted and adjusted Cox proportional hazard ratios were also derived (Table 4). Significant differences in duration of therapy were noted between groups, with a median duration of linezolid therapy of 7 days (IQR, 4–12 days) compared with a median duration of daptomycin therapy of 11 days (IQR, 5–14; *P* < .001). However, even after controlling for duration of therapy and other factors, linezolid treatment remained significantly associated with mortality (Table 4). Factors associated with 30-day mortality are reported in Supplementary Table 3.

The treatment groups were statistically balanced with regard to baseline characteristics following propensity score matching (Supplementary Table 4). In this analysis, treatment failure remained significantly more common in the linezolid-treated group (54.5% vs 45.5%; *P* = .019), which was driven primarily

Table 1. Baseline Patient Characteristics by Antimicrobial Treatment for Vancomycin-Resistant *Enterococcus* Bloodstream Infection

Characteristic	Linezolid (n = 319)	Daptomycin (n = 325)	*P* Value
Age, y, median (IQR)	67 (59–76)	64 (58–74)	.192
Age ≥65 y	175 (54.9)	150 (46.2)	.027
Male sex	309 (96.9)	321 (98.8)	.098
Body mass index, kg/m^2, median (IQR)	25.5 (21.8–31.1)	26.1 (22.6–31.0)	.336
Enterococcus faecium	276 (86.5)	263 (80.9)	.055
Enterococcus faecalis	24 (7.5)	25 (7.7)	.936
Other VRE species or unspecified	19 (6.0)	37 (11.4)	.015
Polymicrobial bacteremia[a]	19 (6.0)	30 (9.2)	.117
Concomitant broad-spectrum antipseudomonal β-lactam treatment[b]	200 (62.7)	192 (59.1)	.347
Infection source			
Line	109 (34.2)	134 (41.2)	.065
Genitourinary	35 (11.0)	27 (8.3)	.252
Abdominal	39 (12.2)	44 (13.5)	.619
Gastrointestinal	43 (13.5)	17 (5.2)	<.001
Endocarditis/cardiac device	10 (3.1)	29 (8.9)	.002
Wound/bone	22 (6.9)	15 (4.6)	.214
Unknown	61 (19.1)	59 (18.2)	.752
Source control[c]			
Yes	188 (72.9)	207 (77.8)	.188
No	16 (6.2)	14 (5.3)	.644
Undocumented	54 (20.9)	45 (16.9)	.241
Facility complexity level[d]			
1a	138 (43.3)	193 (59.1)	<.001
1b	77 (24.1)	104 (32.0)	.026
1c	97 (30.4)	26 (8.0)	<.001
2	4 (1.3)	3 (0.9)	.723
3	3 (0.9)	0 (0.0)	.121
Solid organ transplant	18 (5.6)	32 (9.8)	.046
Kidney	11 (3.4)	14 (4.3)	.572
Liver	5 (1.6)	17 (5.2)	.015
Heart-lung	2 (0.6)	1 (0.3)	.621
Time to VRE-BSI[e], d, median (IQR)	5 (2–14)	5 (1–15)	.970
Time to treatment[f], h, median (IQR)	83 (55–107)	72 (38–102)	.124
>1 d of VRE-positive blood cultures prior to treatment	46 (14.4)	46 (14.2)	.923
Intensive care unit admission	267 (83.7)	229 (70.5)	<.001
No. of follow-up blood cultures, mean ± SD	1.45 ± 0.89	1.39 ± 1.02	.551
Sepsis	208 (65.2)	210 (64.6)	.768
Charlson comorbidity index, median (IQR)	9 (7–11)	9 (7–11)	.448
Past myocardial infarction	76 (23.8)	69 (21.2)	.431
Congestive heart failure	112 (35.1)	125 (38.5)	.378
Peripheral vascular disease	109 (34.2)	77 (23.7)	.003
Cerebrovascular disease	86 (27.0)	89 (27.4)	.903
Dementia	35 (11.0)	37 (11.4)	.868
Chronic obstructive pulmonary disease	150 (47.0)	143 (44.0)	.441
Rheumatoid arthritis	12 (3.8)	10 (3.1)	.632
Mild liver disease	38 (11.9)	42 (12.9)	.697
Diabetes, uncomplicated	62 (19.4)	82 (25.2)	.078
Diabetes, with end-organ damage	61 (19.1)	80 (24.6)	.092
Hemiplegia	31 (9.7)	26 (8.0)	.443
Moderate or severe renal disease	214 (67.1)	235 (72.3)	.149

Table 1 continued.

Characteristic	Linezolid (n = 319)	Daptomycin (n = 325)	*P* Value
Any malignancy	122 (38.2)	135 (41.5)	.393
Severe liver disease	28 (8.8)	50 (15.4)	.010
Metastatic solid tumor	29 (9.1)	27 (8.3)	.724
HIV infected	5 (1.6)	3 (0.9)	.460
Peptic ulcer disease	31 (9.7)	33 (10.2)	.853
Hematologic malignancy	38 (11.9)	63 (19.4)	.009
Neutropenia	39 (12.2)	62 (19.1)	.017
Acute kidney injury	143 (44.8)	154 (47.4)	.515
Mechanical ventilation	70 (21.9)	37 (11.4)	<.001
Thrombocytopenia	34 (10.7)	41 (12.6)	.439
APACHE II score, median (IQR)	16 (12–21)	14 (10–20)	.005

Data are presented as No. (%) unless otherwise specified. Categorical variables compared by χ^2 or Fisher exact test. Continuous variables compared by Mann–Whitney *U* test or *t* test.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BSI, bloodstream infection; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; VRE, vancomycin-resistant *Enterococcus*.

[a] ± 72 hours of index VRE blood culture.

[b] At least 1 dose of cefepime, ticarcillin-clavulanate, piperacillin-tazobactam, meropenem, doripenem, or imipenem-cilastatin following positive VRE blood culture.

[c] Comparison among those with a known source of infection (linezolid, n = 258; daptomycin, n = 266).

[d] Facility complexity designation at the time of index VRE blood culture. Facility complexity levels are based on patient population, complexity of clinical services, and education/research, with level 1a designated as the most complex.

[e] Time from beginning of hospitalization to first positive VRE blood culture.

[f] Time from index VRE blood culture to first dose of linezolid or daptomycin.

by differences in mortality and microbiologic failure (Supplementary Table 5). Overall, outcomes in the propensity score–matched cohort were consistent with other analyses.

Table 2. Clinical Outcomes by Antimicrobial Treatment for Vancomycin-Resistant *Enterococcus* Bloodstream Infection

Outcome	Linezolid (n = 319)	Daptomycin (n = 325)	Risk Ratio (95% CI)	*P* Value
Treatment failure	214 (67.1)	178 (54.8)	1.37 (1.13–1.67)	.001
30-day all-cause mortality	137 (42.9)	109 (33.5)	1.17 (1.04–1.32)	.014
Microbiologic failure[a]	23 (14.6)	15 (6.4)	1.10 (1.02–1.18)	.011
60-day VRE-BSI recurrence	80 (25.1)	72 (22.2)	1.04 (.96–1.14)	.347
Early (7-day) mortality	41 (12.9)	23 (7.1)	1.07 (1.01–1.12)	.016
Hospital length of stay, d, median (IQR)	14 (7–25)	12 (6–25)	. . .	.228
Duration of bacteremia, d, median (IQR)	4 (2–7)	3 (2–5)	. . .	.033

Data are presented as No. (%) unless otherwise specified. Reference group: linezolid treatment.

Abbreviations: CI, confidence interval; IQR, interquartile range; VRE-BSI, vancomycin-resistant *Enterococcus* bloodstream infection.

[a] Percentages among those with ≥1 follow-up blood culture drawn during treatment period (linezolid, n = 157; daptomycin, n = 233).

The association between linezolid treatment and 30-day all-cause mortality persisted after stratifying by VRE-BSI species (*E. faecium* vs *E. faecalis*; Mantel–Haenszel common RR, 1.16; 95% CI, 1.01–1.32; *P* = .027). Among those with VRE-BSI caused by *E. faecium*, the RR for 30-day all-cause mortality was 1.14 (95% CI, 1.00–1.31) compared with 1.28 (95% CI, .89–1.85) among infections caused by *E. faecalis*. Linezolid treatment was also associated with 30-day all-cause mortality stratified by source of infection (line vs nonline; Mantel–Haenszel common RR, 1.16; 95% CI, 1.03–1.31; *P* = .016). Among those with a line source of VRE-BSI, the RR for 30-day all-cause mortality

Table 3. Poisson Regression of Factors Associated With Treatment Failure Among Patients With Vancomycin-Resistant *Enterococcus* Bloodstream Infection

	Unadjusted		Adjusted	
Factor (N = 644)	Risk Ratio (95% CI)	*P* Value	Risk Ratio (95% CI)	*P* Value
Linezolid treatment	1.37 (1.13–1.67)	.001	1.15 (1.02–1.30)	.026
Intensive care unit admission	1.67 (1.34–1.96)	<.001	1.31 (1.08–1.60)	.007
Severe liver disease	1.60 (1.08–2.36)	.009	1.19 (1.03–1.37)	.016
APACHE II score	1.04 (1.03–1.05)	<.001	1.03 (1.02–1.03)	<.001

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval.

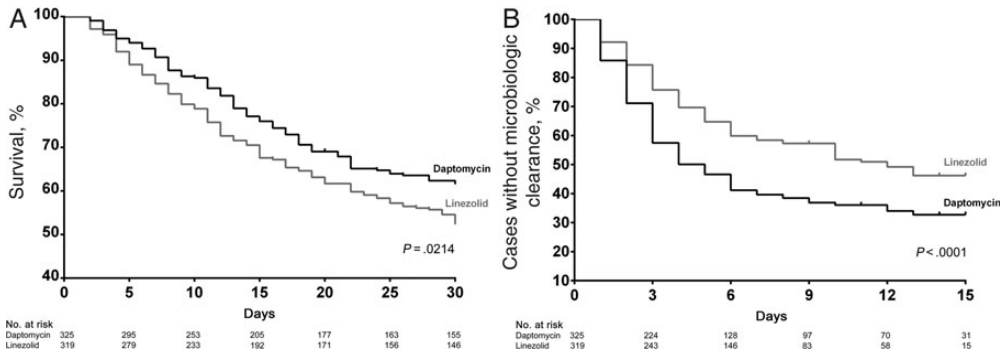

Figure 1. Kaplan–Meier curves for outcomes (*A*) 30-day mortality and (*B*) microbiologic failure.

was 1.14 (95% CI, .94–1.39), and among those with a nonline source of infection, the RR for 30-day all-cause mortality was 1.17 (95% CI, 1.01–1.37).

We conducted an analysis of daptomycin-treated subjects with or without concomitant β-lactam or aminoglycoside treatment. Only agents that have been shown to be synergistic against some VRE strains in previous in vitro experiments were included [27]. These agents included ampicillin or ampicillin-sulbactam (n = 14), aztreonam (n = 13), cefazolin (n = 10), cefepime (n = 62), cefotaxime (n = 4), ceftazidime (n = 18), ceftriaxone (n = 35), imipenem-cilastatin (n = 49), doripenem (n = 8), ertapenem (n = 17), meropenem (n = 33), piperacillin-tazobactam (n = 96), ticarcillin-clavulanate (n = 10), amikacin (n = 10), tobramycin (n = 10), and gentamicin (n = 27). Unexpectedly, patients treated with a concomitant β-lactam agent appeared to have a higher proportion of treatment failure (56.3% [n = 135/240] vs 50.6% [n = 43/85]); however, this association was not statistically significant ($P = .367$). This relationship was also true for concomitant aminoglycoside therapy and treatment failure (57.8% [n = 26/45] vs 54.3% [n = 152/280]; $P = .662$).

Table 4. Cox Proportional Hazards Model of Factors Associated With 30-Day Mortality Among Patients With Vancomycin-Resistant *Enterococcus* Bloodstream Infection

Factor (N = 644)	Hazard Ratio (95% CI)	*P* Value
Linezolid treatment	1.36 (1.05–1.76)	.021
Age ≥65 y	1.27 (.97–1.67)	.088
Intensive care unit admission	1.90 (1.29–2.80)	.001
Severe liver disease	1.83 (1.26–2.66)	.002
Hematologic malignancy	1.57 (1.11–2.22)	.011
Thrombocytopenia	1.52 (1.07–2.16)	.019
Unknown infection source	1.69 (1.25–2.28)	<.001
APACHE II score	1.03 (1.01–1.05)	<.001

Cases right-censored at end of treatment period.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval.

Adverse Events

The frequency of adverse events compared by antimicrobial treatment group is displayed in Table 5. Of the 569 patients with platelet measurements available during the treatment period (linezolid, n = 285; daptomycin, n = 284), thrombocytopenia occurred more frequently among those treated with linezolid (6.3% vs 4.9%). However, no statistically significant association between VRE-BSI treatment and development of thrombocytopenia was observed (odds ratio [OR], 1.30; 95% CI, .60–2.87; $P = .593$). Among the 275 patients with CPK measurements available during the time period evaluated, CPK elevation was observed in 6 of 211 daptomycin-treated patients (2.8%) and 1 of 64 linezolid-treated patients (1.6%; OR, 0.54; 95% CI, .01–4.61; $P = .974$).

DISCUSSION

The purpose of this study was to compare the safety and effectiveness of linezolid and daptomycin for the treatment of VRE-BSI. To our knowledge, this is the first nationwide cohort study comparing these agents and the largest single investigation to date. Treatment with daptomycin resulted in significantly less treatment failure, 30-day mortality, microbiologic failure, 7-day mortality, and duration of bacteremia. The mortality rates we observed were consistent with previous studies of VRE-BSI [25]. However, the present study is the first to demonstrate improved clinical outcomes associated with daptomycin treatment.

Consistent with previous studies, microbiologic clearance was common and occurred in 90.0% of cases overall [25]. Microbiologic clearance is especially important in critically ill and neutropenic patients, and a shorter duration of bacteremia corresponds with better survival in this population [6]. Previous researchers hypothesized that treatment with a bactericidal agent such as daptomycin may lead to improved clinical outcomes, but this had not been demonstrated prior to the present study [9, 25]. As can be interpreted from the associated Kaplan–Meier curves (Figure 1), the effect of daptomycin treatment on

Table 5. Adverse Events by Antimicrobial Treatment Group for Vancomycin-Resistant *Enterococcus* Bloodstream Infection

Outcome	Linezolid	Daptomycin	Odds Ratio (95% CI)	*P* Value
Thrombocytopenia, No. (%)	18/285 (6.3)	14/284 (4.9)	1.30 (.60–2.87)	.593
Creatine phosphokinase elevation, No. (%)	1/64 (1.6)	6/211 (2.8)	0.54 (.01–4.61)	.974

Reference group: linezolid treatment. Adverse events compared by logistic regression.

Abbreviation: CI, confidence interval.

microbiologic clearance appeared to be greatest within the first 3–7 days of treatment. This finding corresponds with the improved early mortality benefit with daptomycin treatment we observed, which may be a result of the rapid bactericidal activity of daptomycin in comparison to linezolid.

Multiple retrospective studies have aimed to compare clinical outcomes between linezolid and daptomycin for VRE-BSI, but have failed due to inadequate sample sizes [20–23]. Recently, researchers have pooled data from these investigations [24, 25]. In direct contrast to the present study, one of these meta-analyses reported improved survival measured by overall mortality, defined as a composite of 7-day, 30-day, hospital, and infection-related mortality, among those treated with linezolid [24]. Significant limitations associated with this meta-analysis may have resulted in misinformed conclusions. Most important, there were profound differences in inclusion and exclusion criteria across studies that would lead to a heterogeneous study population.

Previous data suggest that VRE-BSI recurrence may be higher among daptomycin-treated subjects [22]. This finding has been attributed to the increased use of daptomycin among immunosuppressed patients [22, 25]. Although more patients with hematologic malignancy and neutropenia were treated with daptomycin in the present study, we did not observe an increase in VRE-BSI recurrence. The reason for this is unclear, but may be related to more accurate patient follow-up within the integrated Veterans Affairs healthcare system.

In the present analysis, daptomycin consistently performed better than linezolid in all the clinical outcomes evaluated, whereas no differences in adverse events were observed. Of note, we only collected objective laboratory data during the treatment period as part of our safety evaluation. Side effects such as myalgias may manifest in the absence of CPK elevation and may differ between treatment groups [28]. However, the frequency of CPK elevation we observed was consistent with previous analyses [26].

Synergy with daptomycin has been demonstrated with multiple β-lactam and aminoglycoside agents against VRE, although this effect is not observed with all strains [27]. In this cohort, addition of a β-lactam agent or aminoglycoside to daptomycin did not appear to significantly reduce treatment failure. Because we were unable to analyze the synergistic activity of these combinations, it is impossible to conclude if this observation was due to nonsuperiority of combination therapy or some other factor. It is important to note that this study was not designed to evaluate the effect of daptomycin combinations on clinical outcomes.

A number of considerations should be taken into account to appropriately interpret the data from the present study. First, this was a retrospective observational study and suffers from the limitations of this design. Second, microbiologic failure and duration of bacteremia are largely dependent on the timing of follow-up cultures, which may vary based on individual patient condition and between practitioners. Third, susceptibility data were not reported for the majority of cases. However, due to rarity of linezolid resistance and daptomycin nonsusceptibility among VRE isolates, we do not anticipate that this would have a significant impact on our findings [29, 30]. Fourth, standard 6 mg/kg doses of daptomycin were used in the majority of patients, despite newer evidence that higher doses may lead to better outcomes in patients with VRE-BSI [15–17]. High-dose daptomycin (>8 mg/kg) was only used in 4.3% of subjects, preventing an analysis of the effectiveness of these doses. However, our findings likely underestimate the treatment difference between daptomycin and linezolid because of the lower daptomycin doses utilized. Additionally, data on VRE colonization, infectious diseases specialist consultation, and time to positivity were not available at the time of this study and could not be considered in analyses. Although data on hematologic malignancy and neutropenia were collected, hematopoietic stem cell transplant status was not assessed. Last, we were likely underpowered to evaluate differences in the observed proportions of 60-day VRE-BSI recurrence and adverse events in respective subsets.

In summary, treatment with linezolid rather than daptomycin for VRE-BSI resulted in significantly greater treatment failure. The association between treatment failure and linezolid treatment persisted even after adjusting for confounding factors in Poisson regression and propensity score matching. In a Cox proportional hazards model, treatment with linezolid was also associated with lower 30-day survival compared with daptomycin. Overall, daptomycin treatment for VRE-BSI appeared to result in better clinical outcomes than linezolid.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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