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Comparison of linezolid and daptomycin for the treatment of vancomycin-resistant enterococcal bacteremia

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Abstract: Vancomycin-resistant enterococcal bacteremia (VRE-B) is a common nosocomial infection associated with significant morbidity and mortality. Daptomycin and linezolid are primary treatment options although definitive clinical data to assess comparative therapeutic effectiveness are lacking. This study assessed the outcomes of patients with VRE-B treated with linezolid or daptomycin. This was a single-center, retrospective cohort study evaluating adult patients with VRE-B treated with either daptomycin or linezolid admitted between January 2012 and August 2016 at a tertiary care, academic medical center. The primary outcome was clinical failure, a composite outcome defined as 14-day in-hospital mortality, microbiologic failure, or relapse of VRE-B. Secondary outcomes included 14-day in-hospital mortality, microbiologic failure, relapse of VRE-B, duration of VRE-B, and antibiotic failure. A multivariate logistic regression model was performed to adjust for potential confounding variables. A total of 93 patients were included ($n = 62$ for linezolid and $n = 31$ for daptomycin). All blood isolates were *Enterococcus faecium*. Overall clinical failure was 55.9% and 14-day in-hospital mortality was 21.5%. There was a significantly higher rate of clinical failure in the daptomycin group as compared with the linezolid-treated patients (74.2% *versus* 46.8%; $p = 0.01$; respectively). In multivariate logistic regression analysis, there was a significantly higher odds of clinical failure for patients treated with daptomycin as compared with linezolid (adjusted odds ratio 2.89; 95% confidence interval 1.08–7.75) after adjusting for confounders. Secondary outcomes were not statistically significantly different between study groups. Standard-dose (6 mg/kg) daptomycin treatment was associated with a higher rate of clinical failure as compared with linezolid treatment.

Keywords: daptomycin, minimum inhibitory concentration, linezolid, VRE bacteremia

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Introduction

Vancomycin-resistant enterococcal (VRE) bacteremia (VRE-B) is an increasingly prevalent nosocomial infection worldwide with limited treatment options. It is associated with significant mortality, excess length of hospitalization, and rising healthcare costs.[1–3] VRE is a leading cause of bacteremia among hospitalized patients especially in those at increased risk of infection which include immunocompromised hosts (e.g. stem cell transplants) and critically ill patients.[2,4]

Currently, there are limited effective agents available to treat VRE-B; these include linezolid and daptomycin as the two most commonly used agents.[5] Guidelines published by the Infectious Diseases Society of America (IDSA) specifically recommend treatment with daptomycin or linezolid for VRE intravascular catheter-related bacteremia.[6] Although the IDSA guidelines are from 2009, these two agents remain the mainstay of therapy today with no clear evidence regarding comparative therapeutic effectiveness.

Linezolid is an oxazolidinone antibiotic with broad Gram-positive bacterial activity including VRE. It is the only antibiotic with a United States Food and Drug Administration (US FDA) approval for treatment of VRE infections, including cases with bacteremia.[7] Early data demonstrated the effectiveness of linezolid for VRE-B with clinical and microbiologic cure rates of 78% and 85%, respectively.[8] Linezolid is bacteriostatic *in vitro* which raises concern for its use for deep-seated infections such as infective endocarditis. Despite these theoretical concerns, some data exist for treatment of VRE infective endocarditis and it is currently recommended as a first-line treatment option, along with daptomycin.[9] Other concerns regarding the use of linezolid include toxicities such as myelosuppression or peripheral neuropathy with long-term therapy, as well as potentially severe drug interactions.[7]

Daptomycin is a lipopeptide antibiotic with potent *in vitro* activity against Gram-positive organisms including bactericidal activity against enterococci. Despite a lack of US FDA approval for VRE, daptomycin is considered a first-line agent for VRE-B.[6,9] Given its *in vitro* activity, clinical data, and its favorable safety profile, daptomycin is frequently used in clinical practice. As with linezolid, there are aspects of daptomycin that warrant consideration for VRE-B including emerging resistance, elevated daptomycin minimum inhibitory concentrations (MICs) that may hinder optimal pharmacodynamic target attainment, and lack of standard dosing for VRE infections.[10] A recent national retrospective cohort study observed that high-dose ($\geq$10 mg/kg total body weight) daptomycin was associated with improved survival and microbiologic clearance in VRE-B as compared with lower dosing regimens including 'standard' dosing (6 mg/kg).[11] Other studies assessing mortality have found similar results in which higher doses of daptomycin are associated with lower mortality for patients with VRE-B.[12,13] The MIC breakpoint for daptomycin (susceptible: MIC $\leq$ 4 mg/l) has also come into question as being too high with a recent multicenter cohort study concluding that daptomycin MICs of 3–4 mg/l are predictive of microbiologic failure.[14]

In several meta-analyses published prior to 2015, the results indicate that linezolid may have improved survival as compared with daptomycin for treatment of VRE-B.[15–17] Many of the studies had significant limitations and a variety of outcome measures. In 2015, a large multicenter observational study was published assessing treatment failure of daptomycin *versus* linezolid among Veterans Affairs patients.[18] Results from this study were contrary to previous meta-analyses and indicated that daptomycin was associated with lower rates of treatment failure, lower mortality and lower microbiologic failure as compared with linezolid. Despite previous published literature, the optimal antibiotic treatment for VRE-B remains undefined. The absence of prospective randomized controlled trials requires further observational studies in vulnerable populations. The aim of our study was to assess the outcomes of patients with VRE-B treated with linezolid or daptomycin.

Methods

Study design and population

We performed a single-center, retrospective cohort study of adult inpatients with VRE-B treated with either linezolid or daptomycin between January 2012 to August 2016 at an academic medical center in New Brunswick, New Jersey, USA. VRE-B was defined as the presence of VRE growth in at least one blood culture and treated with antibiotics accordingly as true infection. Patients were identified by consecutive sampling through the microbiology laboratory database. Demographic, microbiologic and clinical data were abstracted from the hospital electronic medical record. At our institution, MICs were determined by broth microdilution *via* automated susceptibility testing methods [MicroScan (BeckmanCoulter, West Sacramento, CA, USA) January 2012 to July 2015 and BD Phoenix (BD, Sparks, MD, USA) August 2015 to August 2016] as per Clinical and Laboratory Standards Institute standards. Only the first VRE-B episode per patient during the study period was included for analysis. All patients were treated with daptomycin or linezolid for at least 48 h. We excluded patients with polymicrobial blood cultures, treated with antibiotics agents other than linezolid or daptomycin, and treated with combination antibiotic therapy for VRE-B. This study was approved by the Rutgers University Institutional Review Board.

Predictor and outcome measures

The primary predictor of interest was treatment with daptomycin compared with linezolid. Multiple covariates were recorded to adequately describe the study population at our institution as well as to control for potential confounding variables by logistic regression modeling. Covariates included age, sex, weight, hospital onset of bacteremia (at least 48 hours after hospital admission), intensive care unit admission day 1 of index blood culture (ICU day 1), presumed source of infection, presence of central line, hematologic malignancy, neutropenia (absolute neutrophil count <500 cell/mm^3), presence of infective endocarditis, on dialysis, comorbidities (measured by the Charlson comorbidity index), severity of illness (measured by Pitt bacteremia score), infectious diseases consultation, use of corticosteroids (prednisone equivalent of 20 mg for at least 14 days). Additional variables were recorded for exploratory analysis assessing outcomes in daptomycin-treated patients: daptomycin dose (measured as mg/kg) and daptomycin MIC.

The primary outcome measure was clinical failure, defined as a composite of 14-day in-hospital mortality, microbiologic failure (positive blood cultures for $\geqslant$4 days following index blood culture with at least 72 h of effective antibiotic therapy or died with persistently positive blood cultures), or VRE-B relapse (positive blood culture with VRE within 30 days of index blood culture after documented clearance). Secondary outcomes included 14-day in-hospital mortality, microbiologic failure, VRE-B relapse, duration of VRE-B (time from index blood culture to first negative blood culture), and antibiotic failure (addition or change in antibiotic therapy by treating physician not due to simplification of regimen for discharge planning).

Statistical analysis

Descriptive statistics were performed for all variables. Continuous variables were compared using a Mann–Whitney *U* test (for nonparametric distributions) or Student's *t* test. Categorical variables were compared using a Chi-square test. The significance level was set at $p < 0.05$ (two-sided). We performed a logistic regression analysis to estimate the crude odds ratio (OR) and 95% confidence interval (CI). Multivariate logistic regression modeling was done to assess for the presence and magnitude of the association of daptomycin treatment and clinical failure while adjusting for potential confounding variables (reported as an adjusted OR). Any variable in the initial bivariate analysis with a modest association ($p < 0.2$) with both the outcome (clinical failure) and the primary predictor (daptomycin treatment) and theoretical clinical plausibility was entered into the multivariable logistic regression model as a potential confounding variable. Only covariates with *a priori* knowledge of potential confounding was assessed for inclusion in the final regression model. Data analysis was performed using Stata, version 15.0 (StataCorp, College Station, TX, USA).

Results

A total of 93 patients were included in the final analysis. Of these patients, 62 patients were treated with linezolid and 31 patients were treated with daptomycin. All blood isolates were identified as *Enterococcus faecium*. Most patients in both groups were male, ICU day 1 occurred in 22.6% in the linezolid group and 38.7% in the daptomycin group ($p = 0.10$). A large portion of patients in both groups had an underlying hematologic malignancy (linezolid 61.3% *versus* daptomycin 38.7%; $p = 0.07$) and were neutropenic (linezolid 50% *versus* daptomycin 41.9%; $p = 0.46$). An infectious diseases consult was noted for a majority of patients in the linezolid and daptomycin group (95.2% *versus* 87.1%; $p = 0.17$; respectively). Particularly for the daptomycin group, the median dose was 6.1 mg/kg [interquartile range (IQR), 5.9–6.7] and 67.7% of patients had a blood isolate with a daptomycin MIC of 4 mg/l. Summary of baseline demographic and clinical characteristics stratified by treatment groups are shown in Table 1.

Overall clinical failure was 55.9% and 14-day in-hospital mortality was 21.5% in the total study population. There was a significantly higher rate of clinical failure in the daptomycin group as compared with the linezolid-treated patients (74.2% *versus* 46.8%; $p = 0.01$; respectively). Although not statistically significant, 14-day in-hospital mortality, microbiologic failure, and VRE-B relapse were all worse in the daptomycin patients (Table 2). The duration of VRE-B was slightly longer in the daptomycin group *versus* linezolid, but the difference was not statistically significant (3.7 days *versus* 3.0 days; $p = 0.78$; respectively). In the

Table 1. Baseline demographic and clinical characteristics.

Characteristic	Linezolid ($n = 62$)	Daptomycin ($n = 31$)	*p* value
Age, years, mean (SD)	61.5 (15.7)	65.2 (16.8)	0.29
Male, *n* (%)	36 (58.1)	21 (67.7)	0.37
Weight, kg, mean (SD)	80.3 (24.4)	87.1 (19.8)	0.18
Hospital onset bacteremia, *n* (%)	55 (88.7)	23 (74.2)	0.07
ICU day 1, *n* (%)	14 (22.6)	12 (38.7)	0.10
Infection source, *n* (%)			0.16
Not identified	23 (37.1)	19 (61.3)	
Gastrointestinal	12 (19.4)	4 (12.9)	
Catheter-related	20 (32.3)	5 (16.1)	
Other	7 (11.3)	3 (9.7)	
Presence of central line, *n* (%)	37 (59.7)	18 (58.1)	0.88
Hematologic malignancy, *n* (%)	38 (61.3)	12 (38.7)	0.07
Neutropenia, *n* (%)	31 (50)	13 (41.9)	0.46
Presence of infective endocarditis, *n* (%)	3 (4.8)	2 (6.5)	0.75
Dialysis, *n* (%)	10 (16.1)	11 (35.5)	0.04
Charlson comorbidity index, median (IQR)	6 (5-9)	8 (5–9)	0.15
Pitt bacteremia score, median (IQR)	2 (0–4)	2 (0–4)	0.48
Infectious diseases consultation, *n* (%)	59 (95.2)	27 (87.1)	0.17
Corticosteroids, *n* (%)	22 (35.5)	14 (45.2)	0.37
Daptomycin dose, mg/kg, median (IQR)	–	6.1 (5.9–6.7)	–
Daptomycin MIC, mg/l, median (IQR)	–	4 (2–4)	–
Daptomycin MIC of 4 mg/l, *n* (%)	–	21 (67.7)	–

ANC, absolute neutrophil count; ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration; SD, standard deviation.

multivariate logistic regression analysis (Table 3), there was a significantly higher odds of clinical failure for patients treated with daptomycin as compared with linezolid (adjusted OR 2.89; 95% CI 1.08–7.75) after adjusting for ICU day 1.

A *post hoc* exploratory analysis was conducted to assess the association of daptomycin MIC with study outcomes as stratified by daptomycin MIC of 4 mg/l ($n = 21$) *versus* MIC ≤2 mg/l ($n = 10$). There were no statistically significant differences between the two daptomycin MIC groups when assessing rate of clinical failure ($p = 0.61$), 14-day in-hospital mortality ($p = 0.35$), and microbiologic failure ($p = 0.64$).

Discussion

We sought to assess the clinical and microbiologic outcomes of patients with VRE-B treated with

Table 2. Primary and secondary outcomes stratified by treatment group.

Outcome measures	Linezolid ($n = 62$)	Daptomycin ($n = 31$)	*p* value
Clinical failure, *n* (%)	29 (46.8)	23 (74.2)	0.01
14-day in-hospital mortality, *n* (%)	11 (17.7)	9 (29)	0.21
Microbiologic failure, *n* (%)	23 (39.7)	15 (55.6)	0.17
VRE-B relapse, *n* (%)	7 (11.3)	5 (16.1)	0.51
Duration of VRE-B, days, median (IQR)	3.0 (1.8–4.9)	3.7 (2.1–4.9)	0.78
Antibiotic failure, *n* (%)	11 (17.7)	4 (12.9)	0.55

IQR, interquartile range; VRE-B, vancomycin-resistant enterococcal bacteremia.

Table 3. Logistic regression model assessing association of daptomycin treatment and clinical failure.

Characteristic	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Daptomycin	3.27 (1.27–8.43)	2.89 (1.08–7.75)
Linezolid	Reference	Reference

CI, confidence interval; OR, odds ratio.
[a]Adjusted for ICU day 1.

either daptomycin or linezolid. The overall high rate of clinical failure was similar to previously published data but, in contrast our findings suggest daptomycin at standard doses is associated with a higher rate of clinical failure relative to linezolid for VRE-B after adjusting for confounding variables. This differs from previous publications that concluded daptomycin is either similar in effectiveness or superior as compared with linezolid.[18,19] Most notably, Britt and colleagues conducted a large observational study among Veterans Affairs (VA) patients that concluded that daptomycin had a significantly lower rate of treatment failure compared with linezolid. Differences in our conclusion could be related to the different study populations including underlying comorbidities. For example, approximately 15% of the VA patients in the Britt and colleagues study had a hematologic malignancy in contrast with 54% of our sample which may be a more vulnerable population affected by likely suboptimal daptomycin dosing.[18] The secondary endpoints that composed the primary outcome, 14-day in-hospital mortality, microbiologic failure and VRE-B relapse, were all numerically higher in the daptomycin group but not statistically significant. Additionally, the duration of VRE-B was slightly higher in the daptomycin group, but the difference was not statistically significant. This suggests that clinically, daptomycin as given at our institution with standard dosing (~6 mg/kg) but possibly suboptimal, is associated with worse clinical outcomes as compared with linezolid. Our findings are in contrast to the traditional thought that bactericidal agents (i.e. daptomycin) are superior to bacteriostatic agents (i.e. linezolid) for severe invasive infections such as bacteremia although this is a belief with a significant lack of supporting clinical evidence.[18,20] A recent systematic review evaluating clinical effectiveness of bactericidal *versus* bacteriostatic antibiotics demonstrated no intrinsic superiority of bactericidal agents, a finding consistent with our study results and supports the notion to not simply select antibiotics based on the type of *in vitro* activity.[21]

Our observational study was conducted at a tertiary care academic medical center with a large hematology/oncology population including bone marrow transplant patients. A significant portion in both treatment groups had a hematologic malignancy or were neutropenic. Despite concern

of side effects of bone marrow suppression, linezolid-treated patients had a relatively low mortality rate even with a majority of patients possessing an underlying immunocompromising condition. Among Gram-positive bacterial infections, VRE-B is one of the most common in neutropenic cancer patients.[22] Therefore, our results can offer much needed clinical data on treatment approaches and clinical outcomes for this vulnerable group of patients given over 40% of our study population was neutropenic.

Given the daptomycin dose was relatively fixed (~6 mg/kg) in our study, we were able to evaluate the daptomycin MIC as an independent/predictor variable among daptomycin-treated patients. Our *post hoc* exploratory analysis of the daptomycin group demonstrated no significant association of daptomycin MIC and study outcomes. This was not consistent with a previous publication evaluating the impact of daptomycin MIC although our null findings may be due to the limited sample size in the daptomycin group.[14] A lack of association could also be due to the potential unreliability of obtaining an accurate daptomycin MIC (e.g. 2 mg/l *versus* 4 mg/l) with automated susceptibility test systems.[23] This could result in a nondifferential misclassification of the exposure (daptomycin MIC $\leqslant$2 mg/l *versus* 4 mg/l) which would bias the outcome measures towards a null finding. Our goal in providing this analysis was to begin to present evidence assessing the causal pathway of daptomycin treatment for VRE-B and mortality or clinical failure. We hypothesize that higher but 'susceptible' daptomycin MIC, suboptimal daptomycin dosing, and resulting microbiologic failure are mediating factors leading to attributable mortality due to VRE-B. Further studies evaluating high-dose daptomycin *versus* linezolid are necessary to better understand the role of daptomycin dose as well as studies assessing the influence of daptomycin MIC on outcomes for daptomycin-treated cases.

Limitations to our study should be considered to appropriately interpret these findings. First, given the retrospective observational nature of this study, we could not assure that all patients had daily blood cultures that would allow for more accurate determination of duration of bacteremia for research purposes. The timing of follow-up blood cultures was dependent on the treating physician at the time of occurrence. Despite this intrinsic limitation, the high rate of infectious diseases consultation likely provided best practice of drawing follow-up blood cultures as clinically indicated. Second, mortality and relapse of VRE-B were only assessed through inpatient hospitalization at our institution. Lastly, our study had a limited sample size and may have been underpowered to detect differences in study outcomes including our post hoc analysis evaluating impact of daptomycin MIC for daptomycin-treated patients. This is not necessarily a concern for finding significance of the primary outcome given that limited power poses the risk of a false-negative conclusion.

Despite these limitations, our study has multiple notable strengths. First, the high rate of infectious diseases consultation ensured that standards of care for VRE-B patients were met. This helps to limit the influence of factors on outcome measures difficult to evaluate retrospectively, such as proper source control for all patients. Second, susceptibility and MIC data were recorded and evaluated for all daptomycin-treated patients which has not been readily assessed in previous studies.[18] Although the strength of our analysis is limited (*post hoc* exploratory analysis with limited sample size), the daptomycin MIC is a key feature for research consideration given the emerging data that it may be associated with clinical outcomes.[14] Third, although we acknowledge the emerging evidence that higher doses of daptomycin appear to have a survival advantage, the standard dose of daptomycin (6 mg/kg) utilized in our study reflects dosing practices in many clinical settings despite this being likely suboptimal. This dosing is also similar to previous cohort studies which improves consistency to compare and interpret outcomes between studies.[18] Therefore, our results may provide value in its external validity and extrapolation to real-world clinical practice where daptomycin 6 mg/kg is used. Clinicians may consider linezolid over daptomycin at standard doses, given that the effectiveness of daptomycin in our study may be underestimated compared with high-dose daptomycin. Fourth, our population included a large portion of hematologic malignancy patients and many with neutropenia, a high risk, vulnerable population of interest for VRE-B. Lastly, we were able to measure clinical and microbiologic outcomes that may better elucidate mediators of mortality such as microbiologic failure and duration of bacteremia.

In summary, standard-dose (6 mg/kg) daptomycin treatment was associated with a higher rate of clinical failure as compared with linezolid treatment after adjusting for confounding variables. Linezolid treatment may provide clinical benefit for treatment of VRE-B over daptomycin although further studies inclusive of high-dose daptomycin are needed to draw more definitive conclusions for clinical practice.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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