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

James A. McKinnell[1,2] and Cesar A. Arias[3,4]

[1]Infectious Disease Clinical Outcomes Research Unit (ID-CORE), Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, and [2]Torrance Memorial Medical Center, California; [3]The University of Texas Health Science Center, Houston; and [4]Molecular Genetics and Antimicrobial Resistance Unit, Universidad El Bosque, Bogota, Colombia

(See the Major Article by Britt et al on pages 871–8.)

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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

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Correspondence: James A. McKinnell, MD, Infectious Disease Clinical Outcomes Research Unit (ID-CORE), LA-Biomed Research Institute at Harbor-UCLA, 1124 West Carson St, Box 466, Torrance, CA 90502 (dr.mckinnell@yahoo.com).

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underlying literature. The limitations of prior studies included variable case definitions, limited sample size, heterogeneous patient 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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