

Treatment considerations in vancomycin-resistant enterococcal bacteremia: daptomycin or linezolid? A review

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Abstract *Background* Vancomycin resistant enterococcal bloodstream infections are an important cause of morbidity and mortality in hospitalized patients. *Aim of the Review* A search of the literature was undertaken to determine the optimal antimicrobial therapy for the management of vancomycin resistant enterococcal bloodstream infections. *Method* MEDLINE, EMBASE, and the Cochrane Library (unrestricted to time or language) were searched for studies of vancomycin resistant enterococcal bloodstream infections in adults reporting outcomes of direct comparisons of linezolid versus daptomycin on November 26, 2012. Studies of basic science, reviews, commentaries, pharmacologic, epidemiologic, or pediatric

studies, and those studies examining conditions other than enterococcal bacteremia, a single antimicrobial agent or other antimicrobials were excluded. *Results* 226 studies were screened for eligibility and yielded eight studies evaluating a total of 807 patients. Inter-rater agreement was 100 %. Qualitative evaluation of the studies was performed using the Newcastle–Ottawa scale. No randomized controlled trials were identified. All studies were retrospective cohorts and non-randomized. 458 (57 %) patients treated with linezolid and 349 (43 %) with daptomycin were analyzed. Variable comorbidities and severity of illness were described in the included studies and reported here for comparison. *Conclusion* The optimal treatment of vancomycin resistant enterococcal bloodstream infections is yet to be determined. Well-designed prospective studies are needed to lend more convincing evidence regarding choice of antimicrobial therapy for this important multidrug resistant organism.

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Impact of findings on practice statements

- Given the quality and quantity of the available evidence, both linezolid and daptomycin remain alternatives for the treatment of VRE BSI.
- Patient outcomes may differ with the antimicrobial choice depending on severity of illness and underlying comorbidities.
- More robust studies are needed to determine which antimicrobial provides the best outcomes in patients critically ill patients with severe VRE BSIs.

Introduction

The evolution of antimicrobial resistance and the limited number of effective antimicrobials is challenging clinicians worldwide [1]. This is certainly the case with Vancomycin-resistant enterococci (VRE), which were first reported as clinically significant in 1988 [2] and have since been found globally [3–8]. In the United States, enterococci are among the most common organisms causing bloodstream infections (BSIs), representing 9 % of BSIs in the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) study [7] and 10.2 % in the SENTRY program [8]. Clinically, VRE are associated with contamination of hospital environments and colonization of the gastrointestinal tracts of patients for prolonged periods of time [9] and can lead to a wide range of infections from intra-abdominal abscesses to infective endocarditis [10]. Despite a growing body of knowledge, these organisms continue to cause significant morbidity and mortality [11]. Vancomycin resistance has also been shown to have an independent association with mortality in VRE BSIs [12].

Enzymes that help synthesize alternative peptidoglycan precursors to those that would form complexes with vancomycin help *Enterococcus* sp. attain resistance [13]. In clinical practice, antimicrobial agents with alternate mechanisms of action against these bacteria have come into favor. For example, linezolid, tigecycline, and quinupristin-dalfopristin affect protein synthesis at the ribosomal level [14] while daptomycin is thought to act by formation of curved membrane patches that can cause slow leakage of ions and affect the cell wall synthesis mechanisms that ultimately lead to rupture of both the cell membrane and cell wall [15].

Linezolid belongs to the oxazolidinones family and has bacteriostatic activity against most bacteria, including VRE [16]. Daptomycin is a cyclic lipopeptide and also has activity against clinical isolates of VRE [17] with demonstrated in vitro bactericidal activity at appropriate doses with and without coadministration of gentamicin, as demonstrated by pharmacodynamic modeling [18]. Clinically, daptomycin has been studied via the Cubicin Outcomes Registry and Experience (CORE) database by Mohr et al. [19] who found clinical cure in 87 % of VRE infections including Bacteremia. Cases of both linezolid [20, 21] and daptomycin resistance [22] have been reported in clinical isolates of enterococci confirmed by laboratory investigation.

Aim of the review

The aim of this review was to ascertain the optimal treatment of VRE BSI. We focused on linezolid and daptomycin because the literature on treatment of VRE BSI is

dominated by studies comparing these two antimicrobial agents [23–30].

Methods

Search strategy

The Cochrane Library, PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Scopus (<http://www.scopus.com/home.url>) databases were accessed on November 26, 2012. Literature in any language and any year was considered for inclusion to ensure a comprehensive search. Keywords searched included vancomycin, enterococcus, bacteremia, daptomycin, and linezolid. These were combined with the Boolean logic operator ‘AND’ to ensure results inclusive of all terms. The operator ‘OR’ was used between European brand names of medications as search terms and to account for spelling variations. Laboratory studies and studies of methicillin-resistant *Staphylococcus aureus* and children were excluded with the ‘NOT’ operator in the Scopus search to narrow the extensive results. Two independent reviewers screened study titles and abstracts (BS and TG) with 100 % inter-rater agreement.

Data abstraction: inclusion & exclusion criteria

Eligibility criteria for inclusion were for studies to have analyzed outcomes comparing treatment of VRE BSI with daptomycin or linezolid used as the primary intervention. To ensure consistency, only studies in which inclusion criteria mandated BSI as defined by positive blood cultures (regardless of infection source) were considered. With regard to outcomes, studies reporting an endpoint of mortality, clinical cure, or microbiologic cure were included and assessed. Any randomized control trials and cohort study designs were considered while review and opinion articles were excluded. Studies were also excluded if they were primarily pharmacologic, epidemiologic, pediatric, basic science, or did not directly investigate linezolid versus daptomycin. Articles with a primary focus of examining other specific conditions (e.g., skin and soft tissue infections, infective endocarditis, etc.) were excluded.

Data regarding characteristics and outcomes of each of the patient cohorts were manually abstracted for comparison to Microsoft Excel™ by two reviewers once article eligibility was determined (BS and TG). A spreadsheet was created from collected data based upon consistently reported baseline characteristics and comorbidities of the cohorts and three predetermined outcomes that were agreed upon by the reviewers, namely mortality, clinical and microbiologic cure. Further quantitative analysis by means of meta-analysis was also considered.

Table 1 Newcastle–Ottawa Score & investigator-developed scoring^a of studies

Metric	Bio [23]	Crank [24]	Kraft [25]	Mave [26]	McKinnell [27]	Chou [28]	Weinstock [29]	Twillia [30]
Newcastle–Ottawa Score	8	8	7	8	8	8	5	8
Culture diagnosis of VRE BSI	2	2	2	2	2	2	2	2
Clear definition of outcomes	2	2	2	2	2	2	2	2
Bias & confounding assessed	1	1	1	1	1	1	1	1
Outcomes adjusted for covariates	2	2	0	2	0	0	0	0
No conflict of interest	1	2	1	0	1	0	0	1
Total investigator-developed	8	9	6	7	6	5	5	6

^a Where 0 = criteria not met, 1 = criteria partially met, 2 = criteria fully met

Quality assessment

Two independent reviewers (BS and RC) assessed the quality of each article using a five-step investigator-defined metric. Each metric was assessed as a 0, 1, or 2, with 0 signifying criterion not met, 1 signifying partially met, and 2 signifying completely met (Table 1). Assessed metrics included: culture diagnosis of VRE BSI and clear definition of outcomes, adjustment of outcomes for covariates, assessment of bias and confounding, and the authors' conflict of interest.

Given that all of the included papers have cohort study designs, we further evaluated the quality of each article using the three-step metric of the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Although this scale has drawn criticism due to its unknown validity [31], we used it here to conduct a further assessment to the investigator-developed tool. Each metric was assessed as having 0–4 stars. Assessed metrics included selection, comparability, and outcomes with possible maximum scores of 4, 2, and 3 stars respectively.

Results

Search results

The literature search (Fig. 1) produced 18 studies from PubMed and 217 from Scopus. After removal of duplicates, 226 unique studies were identified. For the Cochrane Library, search of the keywords above eliminated any matches. Exclusion criteria eliminated 176 of the 226 articles after title review and another 42 after abstract review. Eight retrospective cohort studies evaluating a total of 807 patients and comparing outcomes of VRE BSIs

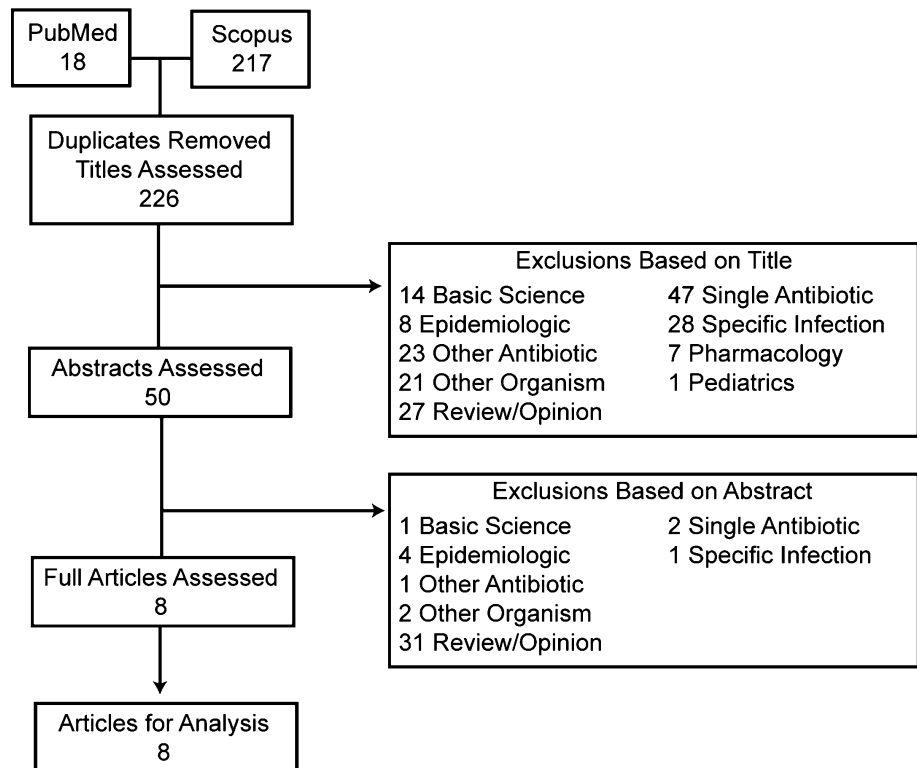
treated with linezolid versus daptomycin were determined to meet all inclusion criteria and analyzed [23–30].

Outcomes

The common outcome assessed in all eight studies was mortality (Table 3). Except for the study by McKinnell et al. [27] which nearly reported statistical significance at $p = 0.052$, none of the studies reported significant p -values for mortality. Mortality was reported as higher in the linezolid group in two studies [23, 25], while the other five studies reported higher mortality in the daptomycin group [24, 26–30].

Microbiological cure rates were examined by three of the studies [23, 26, 30] and reported to be similar between patients receiving the two antimicrobials. Two authors also assessed clinical cure rates; while one [30] found similar cure rates between both antimicrobials, the other [23] reported a higher clinical cure rate with daptomycin (64.7 %) versus linezolid (50 %), ($p = 0.19$).

Other outcomes examined were unique to each particular study. For example, the study by Bio et al. [23] described duration of bacteremia, survival 7 days after end of therapy, length of stay after start of therapy, thrombocytopenia during therapy, and creatine kinase elevations during therapy. The study by Crank et al. [24] assessed duration of positive cultures and number of positive cultures and both the studies by Mave et al. [26] and Twilla et al. [30] assessed relapse of bacteremia. All of these findings were reported with no statistically significant differences, except the assessment of relapse of bacteremia in the study by Twilla et al. [30]. In this study, 12 % of those receiving daptomycin versus 3 % of those receiving linezolid ($p = 0.0321$) had relapse among patients who had follow-up cultures [30].

Fig. 1 Search results

Quality assessment

All eight studies met full criteria for inclusion of patients only with culture diagnosis of VRE BSI with a clear definition of mortality and other outcomes that were identified as a primary or secondary from study outset. None achieved statistical significance for mortality data, but three of the studies adjusted these results for covariates [23, 24, 26]. Bias and confounding were discussed by all studies, but many important elements of selection bias inherent to cohort study design were not assessed even though none of the studies were prospective or randomized. As a result, no included studies completely fulfilled the metric of ‘bias & confounding’ in our quality assessment tool (Table 1). Finally, with the exception of three [26, 28, 29], each study reported at least one author with conflict of interest as defined by present or previous funding or employment by the manufacturing companies of at minimum one of the antimicrobials studied [23–25, 27, 30].

For Newcastle–Ottawa scores, all studies received three stars for the selection metric with the exception of two articles that drew data derived from selected hematology and stem cell transplant patients [25, 29]. All articles received stars for representativeness, selection of the linezolid versus daptomycin-exposed cohorts, and secure record use for attainment of data, and lost a star as they did not investigate whether there were any prior incidences of

VRE BSI in their patient groups (as they were limited by the predetermined timeline of their studies). For comparability, two stars were given to each of the studies except for one which made no direct comparisons, although this was not their stated intention [29]. Finally, for assessment of our principle outcome of mortality, all three stars were awarded for record linkage, adequate length of follow-up (7 days after completion of treatment was considered adequate by reviewers) and for all subjects accounted for. Microbiologic cure and clinical cure were not reported by all studies, so these outcomes were not assessed for quality.

Baseline characteristics

The number of patients who received each antimicrobial agent varied both within and between each study. Notably, the percentage of patients receiving linezolid therapy was larger in all but two of the studies [24, 25]. Each study included a variety of patient comorbidities and all of them attempted to correlate the illness severity before initiation of antimicrobial treatment. Table 2 summarizes the characteristics consistently reported among all included studies. A few of the characteristics were noteworthy. For ICU patients there were statistically significant differences in two studies: the study by Bio et al. [23], reported treatment with linezolid in 87.2 % of the patients compared to daptomycin in 64.9 % ($p = 0.02$); while the study by Mave

Table 2 Baseline patient characteristics reported for patients treated with daptomycin or linezolid for vancomycin-resistant enterococcal bloodstream infections

Characteristic	Antimicrobial agent	First author						
		Bio [23]	Crank [24]	Kraft [25]	Mave [26]	McKinnell [27]	Chou [28]	Twilla [30]
Number of patients	Linezolid	47	34	29	68	104	31	138
	Daptomycin	37	67	43	30	86	16	63
Age	Linezolid	60 (M) [§]	59.6 (m)	–	60 (M) [§]	54.5 (m)	72.2 (m)	60 (m) [§]
	Daptomycin	59 (M)	57.5 (m)	–	51 (M) [§]	50.1 (m)	68.3 (m)	53 (m) [§]
Male sex	Linezolid	46.8	52.9	–	44.1	40	54.8	43
	Daptomycin	46	59.7	–	53.3	48	75	57
ICU stay	Linezolid	87.2 [§]	50	27.6 ^c	29.4 [§]	41	–	–
	Daptomycin	64.9 [§]	43.2	27.9 ^c	53.3 [§]	38	–	–
African American or Black Race	Linezolid	–	–	–	55.9	45	–	75
	Daptomycin	–	–	–	56.7	48	–	62
Transplant	Linezolid	12.7 ^a	44.1 ^b	–	19.1 ^a	15 ^b	–	6 ^a
	Daptomycin	16.2 ^a	41.7 ^b	–	13.3 ^a	16 ^b	–	13 ^a
<i>E. faecium</i>	Linezolid	N/A	94.1	–	97.1	99	–	76
	Daptomycin	N/A	88.1	–	93.3	99	–	84
Malignancy	Linezolid	10.6 ^a	–	–	–	27 ^b	22.6	33 ^b
	Daptomycin	13.5 ^a	–	–	–	37 ^b	43.8	59 ^b
Charlson (mean score)	Linezolid	5.1	–	–	N/A	5	4.3	–
	Daptomycin	4.6	–	–	N/A	4.6	4.6	–
APACHE II (score)	Linezolid	18 (M)	–	–	15 (m)	–	–	–
	Daptomycin	15 (M)	–	–	12.5 (m)	–	–	–
DM	Linezolid	–	–	–	48.5	37	54.8	44
	Daptomycin	–	–	–	36.7	37	50	33
COPD	Linezolid	–	–	–	10.3	–	16.1	6
	Daptomycin	–	–	–	16.7	–	12.5	3
Concomittant Bacteremia	Linezolid	–	–	17.2	50	–	–	–
	Daptomycin	–	–	29.5	66.7	–	–	–
Mean length of stay (in days)	Linezolid	48	43	42.6	–	–	74.9	37.5
	Daptomycin	44	37.1	40.7	–	–	49.9	40.8
ANC < 500/mm ³	Linezolid	0	–	–	–	8 [§]	–	–
	Daptomycin	1	–	–	–	29 [§]	–	–

Values reported as percentages unless noted, values not reported are marked with a dash while N/A signifies inconsistency in reporting of data M represents median, while m represents mean values reported

[§] $p \leq 0.05$

^a Solid organ

^b Solid organ and hematologic

^c Reported for survivors only

et al. [26] reported the use linezolid in 29.4 % and daptomycin in 53.3 % of ICU patients ($p = 0.03$). A larger proportion of patients in the linezolid group was significantly older in two studies [26, 30] and more male patients were treated with daptomycin overall [23–28, 30].

While not explicitly mentioned by some of the other studies, the study by Crank et al. [24] noted that their cohort contained a sizeable portion (31.8 %) of

daptomycin-treated patients that initially received linezolid. Five patients were changed due to treatment failure, four due to intolerance, and twelve due to physician preference [24]. Furthermore, 19.4 % of the same group was also on concurrent treatment with another antimicrobial, such as gentamicin (14.9 %) and rifampin (4.5 %). The study by Weinstock et al. [29] also reported patients whose antibiotics were changed. Finally, we found differences in

Table 3 Included study outcomes

Outcome	Antimicrobial agent	Bio [23]	Crank [24]	Kraft [25]	Mave [26]	McKinnell [27]	Chou [28]	Twilla [30]
Mortality	Linezolid	38.3	29.4	24.1	20.6	26.9	35.5	18
	Daptomycin	32.4	46.3	23.3	26.7	37.2	56.3	24
Microbiologic cure	Linezolid	89.6	–	–	88.2	–	–	94
	Daptomycin	86.5	–	–	90	–	–	94
Clinical cure	Linezolid	50	–	–	–	–	–	74
	Daptomycin	64.7	–	–	–	–	–	75

Values reported as percentages, values not reported are marked with a dash

the comorbidity scoring systems utilized by most studies. The Charlson Comorbidity Index [32] was most commonly used [23, 26–28]. Two of the studies [23, 26] reported APACHE II scores [33].

Discussion

Summary of evidence

The purpose of this review is to uncover whether choice of antibiotic for treatment of VRE BSIs can affect patient outcomes. Our results show that most but not all studies reported a lower mortality in patients treated with linezolid compared to those treated with daptomycin; however, these differences as well as all of the other outcomes evaluated in this review were not statistically significant. Clinical cure was examined by only two of the studies [23, 30] favoring daptomycin, while microbiological cure is less convincing in favor of an antibiotic over the other. Importantly, these differences are likely multifactorial considering that all of the studies published to date and included in this review are retrospective cohorts (Table 3).

Limitations

The most notable limitation of investigating this topic may appear to be the lack of meta-analysis, as given the common assessment of mortality there is potential. Due to the inherent weaknesses found within the retrospective study design of available studies, numerous differences among the cohorts, suspected heterogeneity, and differing definitions of mortality, a meta-analysis was determined to be of little value and not included here. Furthermore, inconsistency in reporting of patient baseline characteristics, illness severity scores, and outcomes was noted. Thus, we could not effectively compare the cohorts and outcomes using current statistical methods.

The cohorts themselves hold many limitations. The data reported by these studies is largely dependent on the assumed accurate record keeping of the clinicians involved with each patient's care. There can be limitations in identifying institutional prescribing practices and susceptibility reporting by microbiology laboratories on the selection of antimicrobials, none of which are evaluated in the studies. Furthermore, there are multiple sources of bias such as: possible selective use of daptomycin in patients who are severely ill to avoid linezolid toxicities, hospital formulary of choice, drug costs or previous linezolid failures.

Conclusion

Differences in outcomes may exist between patients treated with daptomycin or linezolid for VRE BSI, but they cannot be ascertained from currently available literature. Thus, both antibiotics remain feasible options. Clinical insight including patient-specific comorbidities, side-effect profiles, convenience, availability, and costs will continue to be primary determinants of antibiotic choice. Well-controlled prospective studies assessing clinical outcomes are very clearly needed for further guidance.

While this conclusion is unable to help inform clinical judgment, there is much that we can ascertain from these studies to inform future study design. Among these is the need for larger sample sizes, clearer definitions of outcomes, accountability for medication toxicities and contraindications, and the effects of cost and formularies. Collaborations to maximize sample size with use of standardized definitions and appropriate comorbidity scoring systems could better help uncover the optimal antimicrobial therapy for the management of VRE BSIs.

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Conflicts of interest None declared.

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