Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia

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Abstract
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Disciplines
Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

This journal article is available at Research Online: https://ro.uow.edu.au/smhpapers/1470
Is linezolid superior to daptomycin for the treatment of vancomycin-resistant Enterococcus bacteraemia? A systematic review and meta-analysis.

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Running title: Linezolid versus daptomycin for VRE bacteraemia.
Abstract

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

Enterococci are the third most common cause of healthcare-associated bloodstream infections (BSIs) (1). Vancomycin is the first-line treatment of BSIs caused by ampicillin-resistant enterococci; however vancomycin-resistant enterococci (VRE) nowadays account for approximately one third of the enterococcal healthcare-associated infections in the United States (2) and more than 20% in some European countries, respectively. (European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2009. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm:ECDC;2010.http://ecdc.europa.eu/en/publications/Publications/1011_SUR_annual_EARS_Net_2009.pdf). Mortality rates in patients with VRE BSIs range between 20 and 46% (3-5). Patients with BSI due to VRE are 2.5 times more likely to die than patients with BSI due to vancomycin-susceptible strains (6).

Treatment of VRE BSIs is particularly challenging. Those strains are usually resistant to ampicillin (7) and therapeutic options include linezolid, daptomycin, quinupristin-dalfopristin, tigecycline, teicoplanin and telavancin (for which limited clinical data are available). Teicoplanin is not available in the USA and could only be used for some VRE infections (i.e. strains with the VanB -vancomycin-resistant, teicoplanin-susceptible- phenotype and the rare E. gallinarum and E. casseliflavus). Tigecycline does not achieve high serum concentrations and has not been approved for treatment of bacteremias (8). Use of quinupristin-dalfopristin (effective only against E. faecium) is limited by the need of central venous access for administration, frequent side effects and drug interactions (9).

Clinical experience and data for the treatment of VRE BSIs are mainly available for linezolid and daptomycin. Linezolid has been approved by the United States Food and
Drug Administration (FDA) for the treatment of vancomycin-resistant *E. faecium* infections, including those with concurrent bacteraemia. Although daptomycin is not FDA-approved for the treatment of VRE bacteraemia, its rapid bactericidal activity (10, 11) offers an off-label alternative (12, 13). According to the relevant clinical practice guidelines of the Infectious Diseases Society of America, linezolid or daptomycin are recommended for the treatment of catheter-related BSIs caused by ampicillin- and vancomycin-resistant enterococci (14). Limited data exist on the comparative efficacy of daptomycin versus linezolid for enterococcal bacteremias (4, 5). Herein, we summarize the available evidence and provide an estimate on the clinical effectiveness of linezolid versus daptomycin for the treatment of VRE bacteremia, by using meta-analytic methodology.
Materials and Methods

Search Strategy

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

Selection of studies

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

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

Studies identified

The electronic search resulted in the retrieval of 2365 publications (see Fig. S1 in the supplemental material). Their titles were screened to exclude irrelevant studies, resulting in 46 potentially eligible studies. The search of the meetings’ abstracts resulted in the retrieval of eight additional studies. Out of the total 54 studies, 39 were excluded after examining their abstracts (eight retrospective, non-comparative studies, 26 reviews and opinion papers, five irrelevant studies), while four further studies published in meetings proceedings were excluded as they provided data already
included in the identified published full texts (overlapping publications) (15-18). Eventually, eleven studies were considered for further evaluation. One study was excluded at this stage, since daptomycin was not included in the comparator agents (19).

The full reference lists of the studies whose full text was examined were hand-searched, which did not result in the identification of any additional studies, neither did the search of the clinical trials registries. Eventually, ten studies comparing the efficacy of daptomycin and linezolid for the treatment of VRE bacteraemia were included in this systematic review and meta-analysis (4, 5, 20-27).

Data extraction

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

Outcomes

The primary outcome examined in the meta-analysis was mortality, expressed as 30-day all-cause mortality (defined as death from any reason within 30 days from the first culture positive for VRE). Infection-related mortality (defined as death attributed to VRE bacteraemia) and in-hospital mortality (defined as death from any reason during hospital stay) were also evaluated. Since mortality end-points were different across studies, a composite outcome -defined as overall mortality- was also calculated, by including any relevant comparison on mortality rates between daptomycin and linezolid, irrespective of the definition used (i.e all-cause; infection-related; in-hospital; 30-day; etc.). When some data on the outcomes of interest were not provided in the full-text papers or abstracts, the authors were contacted for further information.
Secondary outcome measures included: a) clinical cure (defined as a resolution of signs and/or symptoms of infection after treatment for VRE was discontinued); b) microbiological cure (the last blood culture, drawn after initiation of VRE treatment, being negative); c) recurrence of VRE bacteraemia (a post-treatment blood culture positive for VRE, following at least one negative blood culture); and d) adverse events (defined as the development of an adverse event proven or suspected to be related to the agent used for VRE treatment or to the route of administration).

Quantitative data synthesis
This is presented in detail in the supplemental material.
Results

Systematic review

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

All studies were published between 2005 and 2012 and were of retrospective cohort nature. Two were multicenter studies (21, 27), 7 reported the experience of single centers, whereas in one this information was not provided (26). The primary outcome measure was microbiological cure in two studies (20, 27), 30-day all-cause mortality in one study (4), clinical and microbiological cure in one study (5), while in five studies the primary outcome among those examined was not stated.

The sample size of the included studies ranged from 31 to 201 patients (median 82).

With two exceptions (25, 26), the studies included mixed populations with varying percentages of immunocompromised and non-immunocompromised patients (see Table S2 in the supplemental material).

Definitions of VRE BSIs differed slightly across studies. The Centers for Disease Control (CDC) definition for enterococcal bacteraemia was used in four studies (4, 20, 25, 27). Two or more positive blood cultures or one positive with an identifiable source, in a clinical scenario consistent with bacteraemia, defined VRE bacteraemia in one study (21). The presence of one or more blood cultures positive for VRE (without further clarifications) was used in three studies (5, 22, 24). In the remaining two studies an explicit definition of VRE BSI was not provided (23, 26).

Statistically significant differences in potential confounders between groups of patients treated with daptomycin or linezolid are listed in Table S3 in the...
supplemental material. Adjustments for potential confounders by the authors were performed using multivariable logistic regression analysis in six studies (4, 20-22, 24, 27).

The median daily daptomycin dose was 6mg/kg in six studies (5, 20-22, 26, 27), 5.5mg/kg in one study (25), and dose was not reported in three studies (4, 23, 24). The median duration of treatment ranged between 13 and 15 days in the daptomycin group and between 11 and 15 days in the linezolid group, respectively (20-22, 27). Combination with aminoglycosides was reported in two studies (21, 27). Patients simultaneously treated with more than one anti-VRE agent were excluded in two studies (5, 20) (see Table S4 in the supplemental material).

Prior vancomycin use was reported in two studies (21, 27), being significantly different across groups in one of them (21). Four studies reported inclusion of patients with endocarditis (5, 20, 21, 27). Outcomes of these patients were reported separately from non-endocarditis bacteraemia in one study only (27). Patients were switched from linezolid to daptomycin during treatment of bacteraemia in two studies (due to failure, intolerance or clinical preference (21), and resistance or intolerance (24) respectively) and one patient has switched from daptomycin to linezolid due to adverse events (25). Linezolid susceptibility was tested in three studies (5, 20, 25) and daptomycin susceptibility in two studies (5, 20).
Meta-analysis

Thirty-day all-cause mortality

All-cause mortality at 30 days (our pre-specified primary endpoint) was significantly increased in patients treated with daptomycin as compared to those treated with linezolid (OR: 1.61, 95% CI: 1.08 to 2.40; fixed effects model; heterogeneity: \(p=0.42\)) (Figure 1A). No publication bias was detected (Egger’s test: \(p=0.84\)). Four studies offered data for this outcome (4, 5, 22, 25).

In two studies odds ratios were adjusted for potential confounders in multivariate logistic regression models (4, 22). When these were combined, still a statistically significant increase in mortality rate was present in patients of the daptomycin group as compared to those in the linezolid group (adjusted OR: 2.56, 95% CI: 1.29 to 5.08; fixed effects model; heterogeneity: \(p=0.36\)) (Figure 1B).

Infection-related mortality

Infection-related mortality was significantly higher in patients who received daptomycin compared to linezolid (OR: 3.61, 95% CI: 1.42 to 9.20; fixed effects model; heterogeneity: \(p=0.49\)) (Figure 2A). Adjusted odds ratios for infection-related mortality were not available.

In-hospital mortality

In-hospital mortality rate was significantly higher with daptomycin compared to linezolid (OR: 1.83, 95% CI: 1.05 to 3.20; fixed effects model; heterogeneity: \(p=0.69\)) (Figure 2B). Two studies estimated adjusted odds ratios for in-hospital mortality after controlling for potential confounders in multivariate logistic regression models (21, 27). When these data were combined, higher mortality with daptomycin was
observed, however the difference did not reach statistical significance (OR: 1.65, 95% CI: 0.56 to 4.90; fixed effects model; heterogeneity: $p=0.95$).

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

**Overall mortality**

Overall mortality rate, as defined for the purposes of this meta-analysis, was significantly increased in patients treated with daptomycin compared to linezolid for VRE bacteraemia (OR: 1.41, 95% CI: 1.06 to 1.89; fixed effects model; heterogeneity: $p=0.50$). No publication bias was detected (Egger’s test: $p=0.58$) (Figure 3A).

In the study by Furuya et al. a significant proportion of patients were switched to daptomycin following linezolid failure or intolerance (24). Since this could have potentially resulted in bias, we performed a sensitivity analysis excluding this study, which did not substantially alter the findings (OR: 1.48, 95% CI: 1.09 to 2.00; fixed effects model, heterogeneity: $p=0.54$).

Five studies provided adjusted odds ratios after controlling for potential confounders (4, 20-22, 27). When these data were pooled, overall mortality was still significantly increased in the daptomycin group as compared to the linezolid group (OR: 1.99, 95% CI: 1.19 to 3.32; fixed effects model; heterogeneity: $p=0.71$) (Figure 3B).

**Clinical cure**
A significant difference in clinical cure rate was not detected in patients treated with daptomycin compared to linezolid (OR: 1.04 95% CI: 0.63 to 1.72; fixed effects model; heterogeneity: $p=0.12$). Three studies provided data for this outcome (5, 20, 23).

**Microbiological cure**

Microbiological cure rates did not significantly differ between the two groups (OR: 0.75, 95% CI: 0.41 to 1.39; fixed effects model; heterogeneity: $p=0.76$) (Figure 4A). Six studies offered data on this outcome (5, 20, 22, 23, 26, 27).

**Recurrence of VRE bacteraemia**

There was a trend towards higher relapse rates among patients treated with daptomycin compared to linezolid, the difference marginally failing to reach statistical significance (OR: 2.51, 95% CI: 0.94 to 6.72; fixed effects model; heterogeneity: $p=0.42$) (Figure 4B). Data for this outcome were provided by four studies (5, 20, 26, 27).

**Adverse events**

Notwithstanding the study by Kraft et al. which reported a significant difference in increased liver function tests among patients treated with daptomycin (25), no significant differences in adverse event rates between the two groups were detected, when data from individual studies were combined (see Table S5 in the supplemental material).
Discussion

The present systematic review and meta-analysis summarizes the available data regarding the efficacy of linezolid versus daptomycin for the treatment of VRE bacteremia. To the best of our knowledge this the first study that attempts to critically appraise the existing evidence on this controversial issue. Based on the meta-analysis results, 30-day all-cause mortality was significantly higher among patients with VRE bacteremia who were treated with daptomycin compared to those treated with linezolid. Notably also, the in-hospital mortality and the infection-related mortality rates were also increased in the daptomycin group as compared to linezolid. These findings were not materially altered in the sensitivity analyses (performed by pooling the adjusted odds ratios for mortality that were provided by the authors of individual studies). Administration of both drugs was relatively safe in those high-risk patient cohorts and frequency of adverse events did not seem to differ between the two treatment options.

An important strength of meta-analysis is its inherent ability to increase the statistical power of individual studies. Notably, most of the studies included in this analysis showed a trend towards increased mortality rates among patients treated with daptomycin. With the exception, however, of one study (22), the difference from linezolid did not reach statistical significance. When the results of individual studies were combined, a significant increase in all mortality outcomes in the daptomycin group surfaced, coupled with negligible ($I^2 = 0\%$) heterogeneity across studies. We acknowledge, however, that despite the absence of statistical heterogeneity, significant clinical heterogeneity was present across the studies analyzed (i.e. in terms of patients included, other antibiotics used, doses, etc., summarized in Tables S2-S4). For this reason, the results of the studies were also combined with the use of a random
effects model, and the pooled estimates for all mortality outcomes remained unaltered (data not shown). Hence, the results obtained in this meta-analysis are stable and, thus, they seem to accurately reflect the underlying effect present in the available comparative studies.

In order to further increase the statistical power of this meta-analysis, a composite outcome of overall mortality rate was calculated. This outcome combined data on mortality from individual studies, whether this was expressed as 30-day all-cause mortality (n=4) (4, 5, 22, 25), in-hospital mortality (n=2) (21, 27), infection-related mortality (n=1) (23), mortality at the end of therapy (n=1) (24), mortality at seven days after the end of therapy (n=1) (20), or overall mortality (n=1) (26). The pooled overall mortality rate confirmed the findings of primary analysis.

Certain limitations apply for the interpretation of our results. All available studies were retrospective and observational. The possibility of significant confounders, therefore, exists (e.g. selection bias: patients with worst prognosis being treated with daptomycin; patients able to swallow being treated with linezolid, etc). A proportion of patients treated with either agent were later changed to the other (usually due to failure), had previously received another antibiotic (typically vancomycin) or had additional organisms recovered in blood cultures. Characteristics like the presence of endocarditis (5, 20, 21, 27); source of any secondary bacteraemias (20, 21) (including the –rare- possibility of enterococcal pneumonias, where daptomycin would not be indicated); treating physicians and ID consultations (4); daptomycin dosing (5, 20-22, 25-27); and combination therapies were not available for all patients (21, 27). Although such biases cannot be eliminated outside the context of a randomized prospective trial, we note that results from adjustment that took into account known confounders (listed in Table S3) were all in agreement with those of the primary
analysis. We note in relevance that pooling such patients (i.e. with and without endocarditis; with and without additional therapies, etc) risks in itself introducing bias. Even so, consistent results in favour of linezolid were obtained, when authors of individual studies adjusted for known confounders (4, 20-22, 27). Notably, similar characteristics between the two patient groups were recorded in most studies; in fact factors associated with unfavorable prognosis were over-represented among the linezolid patient group in some studies (i.e. patients being older (4, 5, 27), in ICU (20), or with higher APACHE scores (27). On the other hand, whether daptomycin or linezolid is advantageous in specific patient populations (e.g. haemodialysis, transplant recipients, etc) could not be evaluated in the present study, due to the limited number of data available.

A potential explanation for the observed inferior outcomes of patients treated for VRE bacteremia with a bactericidal agent (daptomycin) than those treated with a bacteriostatic (linezolid) should perhaps be sought in the context of recent reports on daptomycin failures during treatment of enterococcal infections and emergence of resistance especially among VRE strains (28-30). In regards with this, we note the higher (although marginally failing statistical significance) relapse rates of VRE bacteraemia following daptomycin treatment compared to linezolid in our analysis (Figure 4B). In contrast with mortality and tendency of relapses, clinical and microbiological cure rates did not differ between the two agents. Given that neither for mortality causes, nor for clinical/microbiological cure data was available for all studies, a definite conclusion on any relation between those outcomes cannot be drawn with certainty.

Optimal daptomycin dosing for treatment of severe infections remains a challenge, as higher doses have been proposed (29, 31) and recently supported from in vitro data
for VRE (32). Inferences regarding the optimal dose of daptomycin for treating VRE bacteraemia could not be made from this review, since six out of seven studies used a median dose of 6mg/kg (5, 20-22, 26, 27), while one study used a median dose of 5.5mg/kg (25). It is possible that some of the suboptimal outcomes were associated with daptomycin underdosing (i.e < 6mg/kg). Whether even higher, off-label, daptomycin doses would increase efficacy in the treatment of VRE bacteraemia, without increasing toxicity, remains also to be explored. Similarly, the effect of proposed strategies of combination treatment with daptomycin and ampicillin (30) or rifampicin (33) could not be adequately assessed from these data.

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

**Funding**

No funding was received for this study.

**Transparency declarations**

S. Miyakis has received research support, travel grant and honoraria from Pfizer and Novartis. C.A. Venetis and E.P. Balli: no conflicts of interest.
References


Figure 1. Forest plot (using Mantel-Haenszel [M-H] analysis) of unadjusted (A) and adjusted (B) odds ratios for 30-day all-cause mortality among patients treated with linezolid or daptomycin for VRE bacteraemia

A

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<th>Study or Subgroup</th>
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Total (95% CI) 232 311 100.0% 1.61 [1.08, 2.40]

Heterogeneity: Ch^2 = 2.94, df = 3 (P = 0.42); I^2 = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

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Total (95% CI) 100.0% 2.56 [1.29, 5.08]

Heterogeneity: Ch^2 = 0.83, df = 1 (P = 0.36); I^2 = 0%
Test for overall effect: Z = 2.68 (P = 0.007)

Abbreviations: CI, Confidence interval.
Figure 2. Forest plot (using Mantel-Haenszel [M-H] analysis) of odds ratios for infection-related mortality (A), and in-hospital mortality (B) among patients treated with linezolid or daptomycin for VRE bacteraemia

A

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<td>3.61 [1.42, 9.20]</td>
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Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.007)

B

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Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

Abbreviations: CI, Confidence interval.
Figure 3. Forest plot (using Mantel-Haenszel [M-H] analysis) of unadjusted (A) and adjusted (B) odds ratios for overall mortality among patients treated with linezolid or daptomycin for VRE bacteraemia

A

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<th>Study or Subgroup</th>
<th>Daptomycin</th>
<th>Linezolid</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
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<tr>
<td>Bio et al., 2011</td>
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<td>37</td>
<td>18</td>
</tr>
<tr>
<td>Crank et al., 2010</td>
<td>19</td>
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<td>10</td>
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<tr>
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<tr>
<td>El-Lababibi et al., 2007</td>
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<tr>
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</tr>
<tr>
<td>Marion et al., 2006</td>
<td>11</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Mave et al., 2009</td>
<td>8</td>
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<td>14</td>
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<tr>
<td>Mckinell et al., 2011</td>
<td>32</td>
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<tr>
<td>Twilla et al., 2012</td>
<td>15</td>
<td>63</td>
<td>25</td>
</tr>
</tbody>
</table>

Total (95% CI) 408 538 100.0% 1.41 [1.06, 1.89]

Total events 139 138

Heterogeneity: Chi² = 3.90, df = 9 (P = 0.50); P = 0%

Test for overall effect: Z = 2.32 (P = 0.02)

B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log(Odds Ratio)</th>
<th>SE</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
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<td>IV, Fixed, 95% CI</td>
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<td>Bio et al., 2011</td>
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<td>0.06196</td>
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<td>Crank et al., 2010</td>
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<td>Dubrovskaya et al., 2008</td>
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<td>0.74194</td>
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</table>

Total (95% CI) 100.0% 1.99 [1.19, 3.32]

Heterogeneity: Chi² = 2.13, df = 4 (P = 0.71); P = 0%

Test for overall effect: Z = 2.62 (P = 0.009)

Abbreviations: CI, Confidence interval; IV, Inverse variance.
Figure 4. Forest plot (using Mantel-Haenszel [M-H] analysis) for odds ratios for microbiological cure (A) and for bacteraemia recurrence (B) in patients treated with daptomycin or linezolid for VRE bacteraemia

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Daptomycin</th>
<th>Linezolid</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
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<td>Events</td>
<td>Total</td>
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<td>El-Labibiti et al., 2007</td>
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<td>Marion et al., 2008</td>
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<tr>
<td>Mave et al., 2009</td>
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<tr>
<td>Twilla et al., 2012</td>
<td>36</td>
<td>63</td>
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<tr>
<td>Total (95% CI)</td>
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<tr>
<td>Total events</td>
<td>185</td>
<td>305</td>
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</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.90, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.39)

B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Daptomycin</th>
<th>Linezolid</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Biro et al., 2011</td>
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<tr>
<td>Twilla et al., 2012</td>
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<td>3</td>
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<tr>
<td>Total (95% CI)</td>
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<td>232</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
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<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)

Abbreviations: CI, Confidence interval.