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Review

Similar efficacy and safety of daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bloodstream infections: a meta-analysis

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ABSTRACT

Daptomycin and linezolid are the most commonly used antibiotics for bloodstream infection caused by vancomycin-resistant enterococci (VRE-BSI). However, the best therapeutic agent to treat VRE-BSI remains to be established. In order to provide evidence for an optimal treatment decision, a systematic review and meta-analysis was performed comparing the efficacy and safety of daptomycin and linezolid for the treatment of VRE-BSI. After thorough searching of relevant studies from MEDLINE, EMBASE, Clinicaltrials.gov and international meetings up to November 2015, 11 retrospective cohort studies were finally included with a sample size of 1339 patients. Among these 11 included studies, all patients in the daptomycin group received standard or high-dose daptomycin treatment (≥6 mg/kg/day). Data were extracted and pooled risk ratios (RRs) and 95% confidence intervals (95% CIs) were calculated using a random-effects model. The meta-analysis indicated similar crude overall mortality between patients receiving daptomycin and those treated with linezolid (RR = 1.07, 95% CI 0.83–1.37). Moreover, no difference regarding clinical cure (RR = 1.11, 95% CI 0.88–1.42), microbiological cure (RR = 0.99, 95% CI 0.90–1.09) or relapse rate of VRE-BSI (RR = 1.08, 95% CI 0.76–1.52) was found between daptomycin and linezolid. Adverse event rates were not significantly different between the two groups. Currently available evidence indicates similar efficacy and safety of daptomycin and linezolid for the treatment of VRE-BSI. However, the findings in the meta-analysis are limited by heterogeneity between relatively small-scale retrospective studies and should be interpreted cautiously.

1. Introduction

In recent years, vancomycin-resistant enterococci (VRE) have become an increasingly growing microbiological problem in hospital-acquired infections. For example, in the USA, isolation rates of vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* reached 9% and 77%, respectively, in 2013 as a percent of all *Enterococcus* healthcare-associated infections [1]. Bloodstream infection caused by vancomycin-resistant enterococci (VRE-BSI) brings more difficulty to clinical treatment and more life-threatening consequences for patients compared with infections caused by vancomycin-susceptible enterococci [2]. Among the risk factors for death caused by VRE-BSI, co-morbidities probably play an important role especially for immunocompromised patients with haematologic malignancy, neutropenia, liver transplantation or other severe conditions [3–5].

However, current treatment options for VRE-BSI are still limited and include linezolid, daptomycin, teicoplanin, tigecycline, quinupristin/dalfopristin and telavancin. The most widely used antibiotics worldwide in treating VRE-BSI are linezolid and daptomycin. Regarding the other antibiotics mentioned above, drug availability, authority-approved indications, administration route and adverse effects lead to less clinical experience and usage data [6,7]. However, neither linezolid nor daptomycin is perfect based on current knowledge of these two drugs. On the one hand, bone marrow suppression, bacteriostatic activity and resistant VRE strains are challenging problems during linezolid treatment [8,9]. On the other hand, daptomycin has not been approved for the treatment of VRE-BSI although it has been shown to have similar clinical activity to linezolid [10,11].

Researchers have attempted to conduct randomised clinical trials to identify a better antibiotic for VRE-BSI treatment, however they have failed to enrol sufficient subjects [12,13]. Up to now, only a few observational studies have been conducted. Prior to this meta-analysis, three recent meta-analyses all suggested a superior survival benefit of linezolid over daptomycin [14–16]. However, these meta-analyses have some common limitations. One problem is that they

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all included conference abstracts with important information missing (such as outcome definitions and enrolment criteria), which may compromise the quality of data synthesis. For example, these meta-analyses all wrongly included the conference abstract by Marion et al. [17], which was in fact a partial work of the study by Barbour et al. [18]. Another problem is that nearly one-half of patients in all studies had insufficient daptomycin dosing (<6 mg/kg/day) for comparative assessment of all outcomes. Last but not least, they all documented treatment selection bias and significantly different confounders between intervention groups, however none of these meta-analyses conducted a further analysis on the influence of baseline inequality on the meta-analysis results.

In the present meta-analysis, low-quality conference abstracts and data for patients with insufficient daptomycin dosing were excluded, but several other new studies since the publication of the last meta-analysis were included [19–22]. In addition, a 'baseline inequality index' (BII) method was adopted to assess the impact of baseline inequality on the pooled effect size, and a further adjustment was conducted in order to provide a more reasonable estimate of effect value.

2. Materials and methods

2.1. Search strategy

Relevant literature published before 1 November 2015 in MEDLINE, EMBASE, Clinicaltrials.gov and international conference abstracts were thoroughly searched for studies comparing the efficacy and safety of linezolid and daptomycin for the treatment of VRE-BSI. The search terms and strategy adopted for this study are presented in detail in the Supplementary material.

2.2. Selection of studies

Two investigators (MZ and LL) screened the literature for relevance independently. Studies in this meta-analysis met the following inclusion criteria: (i) comparative evaluation of the efficacy of daptomycin versus linezolid in VRE-BSI; (ii) provision of sufficient data regarding mortality, clinical cure rate, microbiological rate, relapse rate or incidence rate of adverse effects; and (iii) inclusion of only patients receiving daptomycin at a dosage of ≥6 mg/kg/day or provision of such data via contact with the corresponding author. Studies investigating only one drug among linezolid or daptomycin as well as case reports or series were excluded.

2.3. Data extraction, analysis and statistical methods

Data from the eligible studies were extracted in duplicate by two investigators (MZ and LL) independently, and a third reviewer (DC) was consulted to reach a consensus if any discrepancy occurred. The detailed methodology for data collection and extraction is described in the Supplementary material.

All of the statistical analyses in the meta-analysis were conducted using RevMan 5.2 (Cochrane Informatics & Knowledge Management Department). The overall pooled risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were estimated using the Mantel–Haenszel method with a random-effects model, which can consider diversity between studies and provide a more conservative estimate of the assessed effect. *Z*-test with a *P*-value of <0.05 was considered to be statistically significant. Cochrane's *Q* test (significance level of $P < 0.1$) and the I^2 statistic (>50% as evidence of significant inconsistency) were used to measure heterogeneity across the included studies. A sensitivity analysis was also conducted to confirm whether the pooling results were robust and reliable.

2.4. Assessment of bias risk and meta-regression analysis

Publication bias was investigated by means of a funnel plot and was analysed by Egger's test. In addition, a 'baseline inequality index' (BII) method proposed by Ahmad et al. [23] was adopted to assess the baseline inequality between daptomycin and linezolid among included studies. A list of baseline characteristics as recognised risk markers of crude mortality was selected as follows: age; Acute Physiology and Chronic Health Evaluation (APACHE) II score; Charlson comorbidity index; intensive care unit stay; mechanical ventilation; shock; haematologic malignancy; neutropenia; thrombocytopenia; solid organ transplant; liver failure; renal failure or requirement for renal replacement therapy; and origin of VRE (community or hospital) [19].

Within each study, and for each marker, we assessed whether the significant confounder or marker mentioned above was higher in the daptomycin group than the linezolid group (scored as +1) or lower (scored as −1). If the values of a marker were equal or not given, they were scored 0. This score was totalled and a random-effects meta-regression was performed with BII as a moderator using statistical programming R software and 'metafor' package and restricted maximum likelihood estimation as a statistical method. A scatter plot was generated to show the meta-regression result and mortality in lnRR format adjusted by BII.

2.5. Outcomes

The primary outcome was crude overall mortality calculated by including any relevant all-cause, infection-related, in-hospital or 30-day mortality. Secondary outcome measures included (i) clinical cure, (ii) microbiological cure, (iii) relapse rate of VRE-BSI and (iv) adverse events.

3. Results

3.1. Identified studies

The literature selection process is summarised in Fig. 1. After screening and retrieving the full-text, 17 studies were considered for inclusion, including 5 conference abstracts and 12 full-length studies. Among the five conference abstracts, the study by Marion et al. [17] was excluded as a partial work of the study by Barbour et al. [18]; and three conference abstracts lacked important information (e.g. daptomycin dosage, outcome definition). We tried hard to contact the authors for data validation but received no reply, therefore these three conference abstracts were excluded [24–26]. Two full-length studies were excluded due to unavailable data of patients receiving daptomycin at a dosage of ≥6 mg/kg/day and lack of reply from the corresponding author [10,27].

3.2. Study characteristics

As shown in Table 1, all of the included studies were retrospective cohorts composed of seven single-centre studies [18,21,22,29–32] and four multicentre studies [11,19,20,28]. Except for the study conducted by Britt et al. with a total sample size of 441 patients [19], all other included studies analysed less than 200 patients. The definition of VRE-BSI and mortality varied among these studies. Crude mortality data were reported in all studies, but not all studies reported microbiological cure, clinical cure, relapse rate and adverse reactions [mainly thrombocytopenia and creatine phosphokinase (CPK) elevation]. The dosage of daptomycin in the included data ranged from 6 mg/kg/day to 11.5 mg/kg/day and the dosage of linezolid used was mainly 1200 mg/day.

Significantly different confounders between the daptomycin group and the linezolid group in the included studies are shown in Table 2.