Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis)

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**CRD summary**
The authors concluded that there were no statistically significant differences in the effectiveness of linezolid and vancomycin for treatment of in-patients with hospital-acquired methicillin resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections. The authors' conclusions and recommendation for further research reflected the evidence presented, but the small number and poor quality of included trials means their reliability is uncertain.

**Authors' objectives**
To compare the effectiveness of two antibiotics (linezolid and vancomycin) for the treatment of hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections in in-patients.

**Searching**
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2007. Reference lists were checked for additional studies. Search terms were reported.

**Study selection**
Randomised controlled trials (RCTs) comparing oral or intravenous linezolid with intravenous vancomycin for the treatment of in-patients with skin and soft tissue infections as a result of hospital-acquired MRSA were eligible for inclusion. Trials needed to report outcomes for both a clinical cure (resolution of symptoms and signs) and a microbiological cure (eradication of MRSA on wound culture).

There was variation across included trials with regard to inclusion criteria, geographic backgrounds (two worldwide, one included 16 countries and one based in the USA), participant age (average ages ranged from 3.47 to 76 years), co-morbidities and co-treatments. Trials reported clinical and/or microbiological outcomes and some trials included length of stay in hospital, drug treatment and outpatient charges, safety and tolerability.

Trial treatment regimens were as follows: for the majority of trials, linezolid (600mg) orally or intravenously every 12 hours or vancomycin (1g) intravenously every 12 hours; for one trial, linezolid 10mg/kg intravenously every eight hours (orally after three days) or vancomycin (1g) intravenous twice daily. Duration of treatment ranged from four to 28 days across trials.

Two reviewers selected studies for inclusion and any disagreements were resolved by discussion.

**Assessment of study quality**
Trials were assessed for risk of bias according to allocation concealment, blinding, intention-to-treat analysis and completeness of follow-up.

Two reviewers independently assessed study validity and any disagreements were resolved through discussion.

**Data extraction**
The number of participants categorised as cured, failure or intermediate/missing in both the intervention and control groups for clinical outcomes (based on resolution of clinical symptoms by a set time) and microbiological outcomes (based on wound culture) were extracted. For clinical cure, the categories of cured and improvement were combined. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for each outcome.

Two reviewers independently extracted data for inclusion.
Methods of synthesis
The pooled risk ratios and corresponding 95% confidence intervals were calculated using the DerSimonian and Laird random-effects meta-analysis. Statistical heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic. The primary analysis did not include randomised patients for whom no outcome data were available. Sensitivity analysis was carried out for: clinical cure to assess the robustness of combining the two categories 'cured' and 'improvement'; methods used to handle missing outcome data using best and worse case scenarios; and for participant age across trials. The potential for publication bias was not assessed because of the small number of included trials.

Results of the review
Four RCTs (n=1,841 patients, range 60 to 1,200) were included in the review. The method of allocation concealment was unclear in three of four included trials, blinding was not carried out in any, intention-to-treat analysis was performed in only one, and completeness of follow-up ranged from 77 to 100%.

There was no statistically significant evidence of a difference in effect for linezolid when compared with vancomycin for both the clinical outcomes (three RCTs, n=174 patients) and microbiological outcomes (three RCTs, n=439 patients). There was evidence of significant statistical heterogeneity for clinical outcomes ($I^2$=81.7% and p = 0.004), but not for microbiological outcomes. However, a trend towards higher effectiveness favouring linezolid was reported. Sensitivity analyses did not alter the conclusions drawn from the primary analysis.

Authors' conclusions
There was no evidence of a statistically significant differences in effectiveness of linezolid and vancomycin for the treatment of MRSA skin and soft tissue infections in hospital in-patients, but there was an observed trend favouring linezolid. There is a need for additional systematic reviews to assess additional outcomes and other MRSA infection sites.

CRD commentary
This review had clearly stated inclusion criteria in terms of participants, study design, interventions and outcomes. The authors searched relevant databases and references lists of relevant literature. Search terms were reported. Unpublished studies were not searched for, so publication bias could not be ruled out. It was unclear whether language restrictions were applied, so there was the potential for language bias. Efforts were made to minimise reviewer bias and error at study inclusion, validity assessment and data extraction stages of the review process.

Methods used to combine data were appropriate. There were some inconsistencies between data in table 1 and in the text for two included trials. There was high heterogeneity between trials for clinical outcomes; this was investigated appropriately. The methodological quality of included trials was difficult to assess due to lack of reporting of methods of randomisation and allocation concealment; this may have impacted on the findings of the review. The authors also reported that the variation across trials for timing of 'test for cure' or equivalent visit, and the length of treatment, may have lead to potential risk of bias.

The authors' conclusions and recommendation for further research reflected the evidence presented, but the small number and poor quality of included trials mean their reliability is uncertain.

The authors noted that all included trials were funded by the pharmaceutical company that manufactures linezolid.

Implications of the review for practice and research
Practice: The authors stated that clinicians need to consider the effectiveness, cost, side-effects, patients' acceptability and route of drug administration for linezolid and vancomycin when choosing a treatment for MRSA and soft tissue infections.

Research: The authors stated that there is a need for additional high quality systematic comparisons of linezolid and vancomycin focusing on other outcomes (such as length of hospital stay, safety and tolerability) and other infections (such as pneumonia or MRSA in general), and for further research to looking at the potential for increased antibacterial resistance.
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