Efficacy and safety of linezolid in methicillin-resistant Staphylococcus aureus (MRSA) complicated skin and soft tissue infection (cSSTI): a meta-analysis

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CRD summary
This review concluded that linezolid appeared to be more effective than vancomycin for microbiological eradication in methicillin-resistant Staphylococcus aureus (MRSA) evaluable patients, but other findings were inconclusive. Interpretation of the authors’ conclusion should take into account the limitations with the review process and inconsistency in the findings.

Authors' objectives
To assess the safety and efficacy of linezolid versus vancomycin for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) complicated skin and soft-tissue infection.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and the International Pharmaceutical Abstracts were searched from inception to March 2009 for articles in English. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared linezolid with vancomycin for the treatment of adults (≥18 years old) with methicillin-resistant Staphylococcus aureus (MRSA) complicated skin and soft tissue infection (with or without other infections/organisms) were eligible for inclusion. Eligible trials were required to evaluate one or more of the following as the primary outcome: resolution of signs and symptoms of infection in clinically evaluable patients; or microbiological eradication in modified intention-to-treat patients or patients in whom MRSA was evaluable. Eligible trials had to include both baseline assessment of patients and a test-of-cure evaluation seven to 21 days after treatment had ended. Trials were also required to report on the following secondary outcomes: mortality, toxicity, and discontinuation rates.

Included trials were of patients with a mean group age ranging between 52 and 68.4 years, and a mean group weight ranging from 50.7 to 86.13kg. The majority of trials included a greater proportion of men. Trials administered 600mg linezolid orally or intravenously every 12 hours, and the comparison groups received 1,000mg vancomycin intravenously every 12 hours. Treatment duration ranged from 9.2 to 13.7 days for linezolid, and from 8.7 to 12.8 days for vancomycin.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
It appeared that two reviewers independently assessed the quality of the included trials including criteria on randomisation, blinding, whether it was multicentre or multinational, sample size, loss to follow-up and discontinuation of trial medication. Discrepancies were resolved through consensus.

Data extraction
Two reviewers independently extracted data on the primary and secondary outcomes to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). Discrepancies were resolved by consensus.

Methods of synthesis
A fixed-effect model, or a random-effects model where there was evidence of statistical heterogeneity, was used to pool odds ratios and their 95% confidence intervals for different types of patients (i.e. clinically evaluable patients, intention-to-treat patients with microbiological eradication, and patients in whom MRSA was evaluable). Statistical heterogeneity was assessed using Cochran's Q and the I² test.
Sensitivity analyses were conducted for each outcome by removing the trial with the most weighting.

Publication bias was assessed using funnel plots and Egger's test.

Results of the review
Five RCTs (n=2,652 patients) were included in the review. Sample sizes ranged from 135 to 1,180 patients. Four trials reported randomisation methods, but none were blinded. All trials reported discontinuation rates, but only two reported loss to follow-up.

Linezolid was statistically significantly more effective than vancomycin in clinically evaluable patients with methicillin-resistant Staphylococcus aureus (MRSA) complicated skin and soft tissue infection (OR 1.41, 95% CI 1.03 to 1.95; five RCTs), but sensitivity analysis resulted in a non-significant result. There was no evidence of statistical heterogeneity ($I^2=0\%$).

Linezolid was statistically significantly more effective than vancomycin in achieving microbiological eradication in intention-to-treat patients (OR 1.91, 95% CI 1.33 to 2.76; three RCTs) and MRSA evaluable patients (OR 2.90, 95% CI 1.90 to 4.41; five RCTs). There was evidence of significant statistical heterogeneity for comparisons in intention-to-treat patients (main comparison $I^2=73.7\%$; sensitivity analyses $I^2=86.5\%$). Use of a random-effects model showed no significant difference between treatments in microbiological eradication in intention-to-treat patients. Sensitivity analysis did not significantly alter the results in MRSA evaluable patients, but in intention-to-treat patients the difference between the two treatments was no longer significant.

There were no statistically significant differences in mortality rates between the treatment groups. Other secondary outcomes varied for each treatment (as reported in the review).

There was evidence of potential publication bias for microbiological eradication in patients where MRSA was evaluable and mortality outcomes, according to the funnel plot, but this was not supported by the Egger's test.

Authors' conclusions
Linezolid appeared to be more effective than vancomycin for microbiological eradication in methicillin-resistant Staphylococcus aureus (MRSA) evaluable patients, but findings were inconclusive for the resolution of infection in clinically evaluable patients and microbiological eradication in intention-to-treat patients.

CRD commentary
The review question and supporting inclusion criteria were clearly defined. The literature search included three databases, but was restricted to the English language, which meant that language bias could not be ruled out. Attempts were made to identify unpublished data, which reduced the possibility that potentially relevant papers were missed. Tests for publication bias were inconsistent. It appeared that validity assessment and data extraction were performed in duplicate, but it was unclear whether this was true for study selection, which meant that reviewer error and bias could not be ruled out completely.

Validity was assessed using appropriate criteria, but none of the trials fulfilled all criteria, and quality was not taken into account in the statistical analyses. Appropriate methods were used to synthesise the data and test for statistical heterogeneity, but findings were inconsistent when using different pooling methods and sensitivity analyses. The authors acknowledged the limitations with the small number of included trials.

The authors' conclusion should be interpreted taking into account the limitations with the review process and the inconsistency in the findings.

Implications of the review for practice and research
Practice: The authors stated that despite the differences found, the importance of clinical assessment as an initial indicator of treatment response remains critical for decision making and should not be subdued by the results. The authors also stated that the results for mortality were for patients with other infections and the results may not reflect
mortality specifically in patients with MRSA complicated skin and soft-tissue infection. The authors also recommended that linezolid is monitored for thrombocytopenia, nausea, and diarrhoea (with anaemia as an optional monitoring parameter).

**Research:** The authors stated that further research is required to investigate the mortality of patients specifically with MRSA complicated skin and soft-tissue infection.

**Funding**
None.

**Bibliographic details**

**PubMedID**
20001574

**DOI**
10.1185/03007990903454912

**Original Paper URL**
http://informahealthcare.com/doi/abs/10.1185/03007990903454912

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Acetamides /adverse effects /therapeutic use; Aged; Anti-Infective Agents /adverse effects /therapeutic use; Drug Resistance, Bacterial /drug effects; Humans; Linezolid; Methicillin-Resistant Staphylococcus aureus /drug effects /physiology; Middle Aged; Oxazolidinones /adverse effects /therapeutic use; Soft Tissue Infections /complications /drug therapy; Staphylococcal Infections /complications /drug therapy; Staphylococcal Skin Infections /drug therapy; Treatment Outcome; Vancomycin /administration & dosage /adverse effects

**AccessionNumber**
12010001177

**Date bibliographic record published**
14/04/2010

**Date abstract record published**
13/10/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.