
Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials

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CRD summary

This systematic review assessed the effectiveness of linezolid for the treatment of infections caused by Gram-positive cocci. The authors concluded that the effectiveness of linezolid in comparison to glycopeptides or β -lactams was greater for the treatment of SSTIs, the same for the treatment of pneumonia, and uncertain for bacteraemia. Linezolid use was associated with an increased risk of thrombocytopenia. The overall conclusions reflected the evidence presented and are likely to be reliable.

Authors' objectives

To determine whether linezolid is more effective than glycopeptides or β -lactams in the treatment of infections caused by Gram-positive cocci.

Searching

Electronic databases PubMed (January 1995 - December 2005), Current Contents and the Cochrane Central Register of Controlled Trials were searched. Search terms were reported. Reference lists of relevant publications were also checked. Only articles in English, French or German were eligible for inclusion.

Study selection

Randomised controlled trials (RCTs) where linezolid was compared to glycopeptides or β -lactams against Gram-positive rods, with or without the use of concomitant antimicrobials, were eligible for inclusion in the review. Primary outcome measures were treatment success ("cure" defined as resolution of all symptoms and signs of infection and "improvement" defined as resolution of two or more of the baseline symptoms or signs of infection), all cause mortality and adverse effects. Secondary outcomes were treatment duration, microbiological assessment and eradication of Gram-positive cocci. Experimental trials, those focusing on pharmacokinetic or pharmacodynamic variables or studies where participants had cancer or neutropenia were excluded.

In included studies, Gram-positive cocci infections comprised suspected methicillin resistant *Staphylococcus aureus* (MRSA), complicated and uncomplicated skin and soft tissue infections (SSTIs), community-acquired and nosocomial pneumonia, and diabetic foot infections (DFI). Demographic characteristics of patients, route of administration and dosage of linezolid varied between studies. Comparator drugs included: vancomycin, semisynthetic penicillin, teicoplanin, ampicillin plus sulbactam, amoxicillin plus clavulanate, clindamycin, cefadroxil, ceftriaxone, cefpodoxime and dicloxacillin.

Two authors independently selected the studies.

Assessment of study quality

The quality of the studies was assessed using a modified Jadad score, which assessed random number generation, double blinding, withdrawals and allocation concealment. The maximum score was 5. RCTs scoring 3 or more points were considered to be high quality and those scoring fewer than 2 points to be low quality. The authors did not state how the validity assessment was performed.

Data extraction

Data were extracted in order to calculate odds ratios (OR) and 95% confidence intervals (CI) for each outcome, by intention to treat (ITT), and those assessed clinically and microbiologically (terms were defined in paper).

Two independent reviewers performed the data extraction and disagreements were resolved through consensus.

Methods of synthesis

Meta-analyses were performed and pooled ORs calculated for all primary and secondary outcomes using the Mantel-

Haenszel fixed-effects model or the DerSimonian and Laird random effects model. Heterogeneity between the studies was investigated using X^2 and I^2 tests. Studies were weighted according to the proportion of information they provided. Publication bias was assessed using funnel plots and Egger's test.

Subgroup analyses were performed on RCTs that included exactly the same drugs or groups of drugs in the comparator group; in children and adults, type of infection (pneumonia, SSTIs and bacteraemia), ITT or clinically assessed, and whether patients were admitted to hospital or not. A sensitivity analysis was also performed that included blinded trials only.

Results of the review

Twelve RCTs ($n = 6,093$) were included in review. The sample sizes ranged from 117 to 1,200. Six studies were rated as high quality. Publication bias was not detected except for the analysis of patients who developed anaemia (Egger's test $p=0.03$).

Overall, linezolid was found to be more effective than glycopeptides and β -lactams in treating Gram-positive cocci infections in clinically assessed patients (3,751 patients, OR 1.41, CI 1.11, 1.81, $p<0.006$).

In regard to different types of infection, linezolid was shown to be more effective than glycopeptides or β -lactams in the treatment of SSTIs (2,261 clinically assessed patients, OR 1.67, CI 1.31, 2.12, $p<0.0001$) and bacteraemia (255 clinically assessed patients, OR 2.07, CI 1.13, 3.78, $p=0.02$). There was however, no difference in treatment success between linezolid and glycopeptides or β -lactams for the treatment of pneumonia (863 clinically assessed patients, OR 1.03, CI 0.75, 1.42, $p=0.84$).

There was no significant difference in mortality between linezolid and glycopeptides or β -lactams (5,162 patients, OR 0.97, CI 0.79, 1.19, p -value not provided). Although linezolid was associated with a non-statistically significant increase in adverse effects overall (4,932 ITT patients, OR 1.40, CI 0.95, 2.06, $p=0.09$), it was associated with a statistically significant increase in thrombocytopenia (4,058 ITT patients, OR 11.72, CI 3.66, 37.57, $p<0.0001$).

Subgroup analyses (blinded studies only, adult participants only, comparison of linezolid to vancomycin only) were also performed.

Authors' conclusions

Linezolid is more effective than glycopeptides or β -lactams in the treatment of patients with Gram-positive SSTIs. Due to limited data, the effectiveness of linezolid in the treatment of bacteraemia was unclear. There was no difference between linezolid and glycopeptides or β -lactams in the treatment of pneumonia. Treatment with linezolid was associated with an increased risk in thrombocytopenia.

CRD commentary

The review addressed a clear question and was supported by appropriate inclusion criteria. A search strategy using appropriate electronic databases was performed. The restriction of including studies in English, French or German means there could be an increased risk of language bias. Furthermore, there was no search for relevant conference proceedings or unpublished studies, which could increase the risk of publication bias. However, publication bias was assessed and found to be minimal. The authors report using methods designed to reduce bias and error in the selection of studies and the extraction of data but not in the assessment of validity. Comprehensive details of all the studies was provided. Appropriate methods were used to pool the results and to investigate for statistical heterogeneity. This was a generally well-conducted review. The authors' overall conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that the possibility of thrombocytopenia, the development of resistance in an era of increasing incidence of multi-drug resistant Gram-positive cocci, and the need to preserve newer antibiotics, are important factors that should limit the use of linezolid to specific patient populations or infections that are difficult to treat with other antibiotics.

Research: The authors did not state any implications for research.

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