Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: focus on the study design

Vardakas KZ, Mavros MN, Roussos N, Falagas ME

CRD summary
The review concluded that vancomycin was as effective as other antibiotics for patients with gram-positive infections such as pneumonia, bacteraemia, febrile neutropenia and skin and (only for high quality studies) soft-tissue infections. Despite poor reporting the review appeared generally well conducted but the reliability of the overall conclusions is unclear as results varied for individual antibiotic comparisons.

Authors' objectives
To evaluate the effectiveness and safety of vancomycin versus other antibiotics in the treatment of gram-positive infections.

Searching
PubMed, Current Contents, EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and ClinicalStudyResults.org were searched to September 2011 with no language restrictions; search terms were reported. References from relevant articles and reviews were searched. Conferences abstracts were searched but relevant trials were not included in the meta-analysis.

Study selection
Randomised controlled trials (RCTs) that compared vancomycin versus another antibiotic for gram-positive infections were eligible for inclusion. Studies needed to assess effectiveness, toxicity or mortality. Trials with masked or unmasked design were included. Experimental studies, studies of pharmacokinetic or pharmacodynamic variables and trials of older antibiotics or beta-lactams were excluded. Hospital admission of patients was not required. Infections were defined using the individual trial definitions. Complicated and uncomplicated skin and soft-tissue infections were included in the meta-analysis. One trial with low treatment duration was excluded. Primary outcomes were treatment success (cure or improvement) in intention-to-treat (ITT) and clinically evaluable populations, all-cause mortality in the ITT population and adverse events. Secondary outcomes were treatment duration (ITT population) and microbiological assessment.

Vancomycin was compared to teicoplanin (20 trials), linezolid (14 trials), telavancin (four trials) and daptomycin, tigecycline, ceftriaxone, ceftobiprole, quinupristin-dalfopristin, dalbavancin and iclaprim in fewer trials. Most studies allowed other concomitant antibiotics. Most studies were of adult patients and three were of children; 22 were of hospitalised patients. Most studies concentrated on one type of infection.

Two independent reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using a modified Jadad scale with five criteria for randomisation, generation of randomised numbers, double-blinding, withdrawals and allocation concealment. The maximum score possible was 5. High quality studies had a score of at least 3 and low quality studies scored 2 or less.

The authors implied that quality data was extracted in the same way as other data.

Data extraction
Data were extracted for the ITT, clinically evaluable and microbiologically evaluable populations. Numbers of patients and events in each group were used to calculate odds ratios (OR) with 95% confidence intervals (CIs).

Two independent reviewers performed the data extraction. Disagreements resolved by discussion among all four reviewers.
Methods of synthesis
Results were pooled to give odds ratios with 95% CIs using a fixed-effect model (Mantel-Haenszel) where there was no significant heterogeneity and a random-effects model (DerSimonian and Laird) where there was significant heterogeneity. Between-study heterogeneity was determined using the $X^2$ test ($p<0.1$ considered significant) and $I^2$ statistic (>40% considered substantial). Publication bias was assessed using Egger's test and visually using funnel plots. Subgroup analyses were performed by type of comparator antibiotic, by infection type (pneumonia, bacteraemia or skin and soft-tissue infections) and for double-blind and open-label trials.

Results of the review
Fifty-three RCTs were identified (17,420 participants, range 21 to 1,897). The mean quality score was 2.7 (median 2, range 1 to 5); 26 trials had a high quality score and there were 21 double-blind trials.

Effectiveness (treatment success or cure): Overall there was no significant difference in effectiveness between comparator antibiotics and vancomycin (OR 1.08, 95% CI 0.98 to 1.18; $I^2$=0%; 41 comparisons) with no significant differences between vancomycin and individual antibiotics. Comparators were as effective as vancomycin for the ITT population and the microbiologically evaluable population but significantly more effective versus vancomycin for the clinically evaluable population (OR 1.14, 95% CI 1.02 to 1.27; $I^2$=12%; 49 comparisons); this result was also significant for single-blind and open-label studies but not for double-blind studies. There were no significant differences in effectiveness overall for febrile neutropenia, pneumonia or skin and soft-tissue infections but linezolid was significantly more effective than vancomycin for skin and soft-tissue infections (OR 1.61, 95% CI 1.07 to 2.43).

Mortality: There was no significant difference in mortality for comparators versus vancomycin (OR 1.09, 95% CI 0.96 to 1.23; $I^2$=0%; 41 comparisons) and no significant differences between vancomycin and individual antibiotics. There was no significant difference for the overall ITT population. Mortality was higher for the comparator antibiotics in single-blind and open-label studies but not for double-blind studies. This significant result was dominated by one open-label study of patients with both gram-negative and gram-positive infections that compared linezolid with vancomycin; the result was no longer significant when it was omitted from the meta-analysis.

Adverse events: There were overall no significant differences in adverse events (OR 1.07, 95% CI 0.90 to 1.28), withdrawals or episodes of recurrent infections for comparators versus vancomycin and no significant differences for the subgroup analyses for double-blind and for single-blind and open-label studies. Results for individual antibiotic comparisons with vancomycin varied in significance.

Authors' conclusions
On the basis mainly of data from open-label trials, vancomycin was as effective as other available antibiotics for patients with gram-positive infections including pneumonia, bacteraemia and febrile neutropenia. Open-label trials of patients with skin and soft-tissue infections showed vancomycin was less effective than linezolid but had a lower mortality rate but this was not evident for double-blind trials or for patients with severe infections. Study design seemed to make a major contribution to the outcome.

CRD commentary
The review addressed a well-defined question in terms of study design, participants, interventions and relevant outcomes. The search was adequate but studies presented as abstracts of conferences were not included. There was reported to be no evidence of publication bias. Study quality was assessed using suitable criteria and was adequate. Efforts were made to reduce error and bias throughout the review process.

Relevant data were provided but without specific details of the age and gender of patients. The synthesis was appropriate. The authors did not present the results in a consistent format, which made it difficult to interpret the findings. The authors recognised effect differences between the higher quality double-blind RCTs and the lower quality open-label and single-blind studies but did not base their overall conclusions on the higher quality study results. The authors noted that a significant number of patients received antibiotics for gram-negative infections (which may have contributed to effectiveness), that several trials did not monitor serum vancomycin levels and a significant number of patients had presumed but not confirmed gram-positive infections.

Despite poor reporting the review appeared to be generally well conducted but the reliability of the overall conclusions
is unclear as results varied for individual antibiotic comparisons.

**Implications of the review for practice and research**

**Practice:** The authors suggested that linezolid may be more effective than vancomycin but may have higher mortality when treating skin and soft-tissue infections. Other antibiotics may be more effective than vancomycin for *S. aureus* infections (particularly linezolid) or MRSA. The availability of alternative antibiotics enables physicians to make a choice based on effectiveness and safety according to individual patient characteristics.

**Research:** The authors made no recommendations for research.

**Funding**
Not stated.

**Bibliographic details**
Vardakas KZ, Mavros MN, Roussos N, Falagas ME. Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: focus on the study design. Mayo Clinic Proceedings 2012; 87(4): 349-363

**PubMedID**
22469348

**DOI**

**Original Paper URL**
http://www.mayoclinicproceedings.org/article/S0025-6196(12)00208-X/abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Bacterial Agents /adverse effects /therapeutic use; Gram-Positive Bacterial Infections /drug therapy; Humans; Randomized Controlled Trials as Topic; Research Design; Vancomycin /adverse effects /therapeutic use

**AccessionNumber**
12012022719

**Date bibliographic record published**
14/11/2012

**Date abstract record published**
05/02/2013

**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.