Antimicrobials for right-sided endocarditis in intravenous drug users: a systematic review

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CRD summary
This review assessed different antimicrobial therapies for isolated native valve right-sided endocarditis in intravenous drug users. The authors concluded that there was no evidence to support any one regimen over another. This cautious conclusion accurately reflects the evidence of clinically heterogeneous and often small trials included in the review and is likely to be reliable.

Authors' objectives
To assess the evidence for the use of antimicrobial treatment in intravenous drug users (IVDUs) with isolated native valve right-sided endocarditis (RSE).

Searching
The following databases were searched up to 2006: MEDLINE (from 1966), EMBASE (from 1980) and the Cochrane Central Register of Controlled Trials (Issue 3, 2006). Grey literature sources including BIOSIS Previews, clinicaltrials.gov and controlled-trials.com were also searched. Eleven journals from the fields of cardiology, general internal medicine and infectious disease were handsearched, as were abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy (1995-2006). References of relevant studies, papers citing relevant studies, major guidelines and review papers were also screened to identify conference abstracts and further unpublished or published studies. In addition, experts and all first authors of included studies were contacted. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) of single or combination antimicrobial therapy using any route of administration in adult inpatients with suspected native valve RSE who were IVDUs were eligible for inclusion. Both short course (2 weeks or less) and long course (over 2 weeks) therapies were eligible for inclusion. Patients with extrapulmonary metastatic complications or concurrent left-sided endocarditis were excluded from the review. The primary review outcome was complete cure, both clinical and microbiological, until the end of follow-up. Detailed definitions of clinical and microbiological cure, and of treatment failure, were reported in the paper.

Included studies assessed a range of single and combination antimicrobial therapies with a concomitant variation in doses and dosing schedules; most drugs were administered intravenously. Studies assessed outcomes between 2 weeks and 6 months post-treatment. The review focused on adults that had all been diagnosed with methicillin-susceptible Staphylococcus aureus.

Three reviewers independently selected the studies for the review. Disagreements were resolved through consensus.

Assessment of study quality
Studies were independently assessed for validity by three reviewers using the following criteria: randomisation, allocation concealment, blinding, and adequacy of follow-up. Studies were rated as being at high, medium or low risk of bias according to whether three or more, one or two, or no criteria were not met. Disagreements were resolved through consensus.

Data extraction
Three reviewers independently performed the data extraction using a pre-piloted standardised form. Disagreements were resolved through consensus. Where possible, data were extracted on patients who completed treatment and follow-up. Where this was not possible, data on all patients were extracted. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for the outcome of treatment failure.

Methods of synthesis

Database of Abstracts of Reviews of Effects (DARE)
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The studies were combined in a narrative synthesis, although it appears that it was planned to use meta-analysis. Studies were grouped by the nature of the comparison in the following categories: single therapy comparison, single versus combination therapies and combination therapy comparison. Differences between the studies were apparent from the synthesis and were further reported in the evidence tables.

**Results of the review**

Seven RCTs (n = 1,032 randomised, n=227 analysed) were included in the review. Four studies were assessed as being at moderate risk of bias and three at moderate to high risk.

Single therapy comparisons (1 RCT): a single small RCT (n=32 analysed) compared long course intramuscular cephalosporin ceforanide with intravenous cefapirin. There was no significant difference between the treatments.

Single versus combination therapy comparisons (4 RCTs): one RCT (n=74 analysed) compared short course cloxacillin and gentamicin with cloxacillin alone; a second study (n=16 analysed) compared short course cloxacillin and gentamicin with long course teicoplanin; a third (n=20 analysed) compared long course oxacillin alone with oxacillin plus gentamicin; a final study (n=15 analysed) compared long courses of trimethoprim and sulfamethoxazole with vancomycin. In no case was there any significant differences in the failure rates.

Combination therapy comparisons (2 RCTs): one small RCT (n=31 analysed) compared short courses of gentamicin plus one of cloxacillin, vancomycin or teicoplanin; a second RCT (n=39 analysed) compared intravenous oxacillin plus gentamicin with oral ciprofloxacin plus rifampicin. No significant differences between the groups were found in either trial.

**Authors’ conclusions**

‘Randomised trial evidence does not support one antimicrobial regimen over another in the treatment of RSE in IVDUs.’ Further research is required.

**CRD commentary**

The review question and the inclusion criteria were clear. The authors searched a number of relevant databases and systematically sought unpublished studies, thereby reducing the likelihood of publication bias and the exclusion of some relevant studies. The authors used methods designed to reduce reviewer bias and error at all stages of the review process, and conducted an appropriate assessment of study validity. In view of the level of clinical heterogeneity, the decision to employ a narrative synthesis appears appropriate. This was a well-conducted review. The authors’ cautious conclusion accurately reflects the heterogeneous evidence of the included studies and is likely to be reliable.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there is a need for a large adequately powered RCT to compare cloxacillin alone versus cloxacillin plus gentamicin in IVDU patients with RSE. They also made detailed recommendations for secondary outcomes which should be assessed. Further research is also required to evaluate out-patient based therapies, aggressive community-targeted services, concurrent rehabilitation programmes and alternative shorter antimicrobial regimens.

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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.