Systematic review and meta-analysis of antibiotic therapy for bone and joint infections
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CRD summary
This review assessed the efficacy of individual antibiotics for the treatment of bone and joint infections in adults. The authors concluded that the evidence from poor-quality studies was inadequate to draw conclusions. The literature search appeared comprehensive and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy of individual antibiotics for the treatment of bone and joint infections in adults.

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, the National Research Register (UK Department of Health), ClinicalTrials.gov and the collection of research studies being conducted at the NIH Clinical Center ('Search Clinical Research Studies Protocol Database') were searched for studies, meta-analyses and protocols of planned and current reviews published between 1966 and 2000; the search terms were stated. Handsearches of issues of journals containing relevant articles, journal supplements, conference proceedings (Interscience Conference on Antimicrobial Agents and Chemotherapy, European Congress of Clinical Microbiology and Infectious Diseases) and drug monographs were also conducted. The reference lists of retrieved studies were checked. Original articles, narrative reviews, and textbooks of bone and joint surgery were searched manually. Seven authors and experts in the field from Europe were contacted for details of unpublished studies, while eight pharmaceutical companies were asked for data on file. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion.

Specific interventions included in the review
Studies that compared two or more different systemic or local antibiotic regimens were eligible for inclusion. The included studies compared a variety of antibiotic drugs with a variety of different control treatments. The studies also included cointervention with many non-protocol regimens. In some studies the patients also received surgical treatment. The review focused on rifampicin combinations, ticarcillin, fluoroquinolones and polymethylmethacrylate (PMMA) gentamicin bead chains. The review also listed other interventions in the identified studies.

Participants included in the review
Studies of adults with bacterial bone and joint infections other than tuberculosis were eligible for inclusion. Studies of diabetic foot infections were included if they described osteomyelitis patients separately. Subsets of patients with bone infections in clinical trials of different infection sites were also included if at least two eligible patients were allocated to each treatment arm. The included studies enrolled heterogeneous populations including diabetics, trauma patients, and patients with acute and chronic Gram-positive and/or Gram-negative infections.

Outcomes assessed in the review
The primary outcome in the review was quiescence of inflammation after at least 12 months (long-term infection control). The studies had to define this as complete resolution of clinical signs and symptoms of infection. Studies were excluded if they reported outcomes as 'good', 'satisfactory' or 'all patients responded to therapy' and did not define these terms. Relapses were classified as treatment failures. The secondary outcomes were cure and improvement at the end of treatment, described as complete or marked reduction of disease severity or an improvement in limb function after the completion or cessation of treatment. Other outcomes assessed were adverse effects and the eradication of initially cultured pathogen in the last obtained specimen from the infection site.
How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

**Assessment of study quality**
The studies were assessed according to the following criteria proposed by the Centre for Evidence-Based Medicine (http://www.cebm.net Accessed July 2005): concealment of randomisation; at least 80% of patients completed follow-up; analysis on an intention-to-treat basis, or sufficient data presented to permit this type of analysis; baseline comparability of the treatment groups; and concise clinical criteria and adequate sampling methods used for the diagnosis of infection. Two reviewers independently assessed validity and resolved any disagreements through discussion with a third author.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Data from studies presented in multiple publications were checked for consistency and the most complete report was included. Binary outcomes were extracted into 2x2 tables.

**Methods of synthesis**

How were the studies combined?
The studies were grouped by the type of drug and combined using a meta-analysis where possible. Pooled weighted effect sizes and 95% confidence intervals (CIs) were calculated using general inverse-variance methods. Absolute risk differences were also calculated; the associated 95% CIs were calculated using the Newcombe-Wilson hybrid score method. Pooled odds ratios (ORs) were calculated, where appropriate, using the fixed-effect Mantel-Haenszel method with variance calculated according to Robbins in the absence of significant heterogeneity. When significant heterogeneity was found, the random-effects model of DerSimonian and Laird was used. Where a meta-analysis was not possible, the studies were combined in a narrative. Publication bias was assessed using a Galbraith radial plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. It was not possible to carry out the planned sensitivity analyses, owing to a lack of adequate data.

**Results of the review**

Twenty-two studies (n=927) were included: 19 RCTs and 3 quasi-RCTs.

Most of the studies were of a poor quality. Methodological problems included small sample sizes, inadequate descriptions of patients and diseases, and the use of concomitant antibiotics.

Rifampicin (1 RCT, 33 patients).

Rifampicin plus ciprofloxacin improved long-term infection control compared with ciprofloxacin alone, but the improvement was not statistically significant (absolute risk difference 28.9%, 95% CI: -0.7, 54.4); the drop-out rates were 33.3% with treatment and 20% with control. Combination treatment with rifampicin increased adverse effects compared with monotherapy (absolute risk reduction 21.1%, 95% CI: -44.9, 6.6).

Ticarcillin (2 RCTs, 31 patients).

Two studies with unbalanced treatment groups showed some improvement in short-term control of bone infections with Pseudomonas species (OR 6.33, 95% CI: 1.2, 33.9). There was no difference at the 1-year follow-up.

Fluoroquinolones (7 studies, 191 patients).
There was no statistically significant difference between oral fluoroquinolones and intravenous beta-lactam drugs in end of treatment infection control (OR 0.8, 95% CI: 0.5, 1.4) or long-term infection control (OR 1.3, 95% CI: 0.8, 2.1). No statistically significant heterogeneity was detected (P=0.19 for both analyses).

Oral fluoroquinolones significantly increased adverse effects compared with intravenous beta-lactam drugs, but significant statistical heterogeneity was found (P=0.004).

The regression analysis found no evidence of publication bias among fluoroquinolone trials.

PMMA gentamicin bead chains (1 RCT).

Of the 384 patients who had surgical debridement of infected bone and were randomised, only 49 patients randomised to beads received beads alone, the rest also received systemic antibiotics.

The RCT showed significantly improved long-term healing with systemic compared with PMMA antibiotic beads in the intention-to-treat analysis (OR 0.5, 95% CI: 0.3, 0.7, P<0.001). There was no significant difference between treatment in a per protocol analysis at the end of treatment (OR 1.1, 95% CI: 0.5, 2.3) or 1-year follow-up (OR 0.9, 95% CI: 0.6, 1.6).

Systemic treatment increased adverse effects compared with local PMMA beads (OR 2.5, 95% CI: 1.5, 4.0, P<0.0001).

Authors' conclusions
The evidence from poor-quality studies was inadequate to draw conclusions.

CRD commentary
The review question was clear in terms of the study design, intervention and participants, and the outcomes used in the review were described. The search was adequate and attempts were made to minimise publication and language biases. The methods used to select the studies and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Two reviewers independently assessed validity, thus reducing the potential for bias and errors. Validity was assessed using specified established criteria and adequate details of each included study were given.

Statistical heterogeneity was assessed and the studies were, in general, appropriately combined in a meta-analysis. The finding of significant heterogeneity for the meta-analysis of adverse effects of oral fluoroquinolones suggests, as the authors correctly stated, that the meta-analysis might not have been appropriate. In summarising the evidence, the authors took account of some of the methodological limitations of the included studies. The authors' conclusions about the inadequacy of the evidence base are 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 future studies should adhere to published guidelines for the conduct of RCTs, as proposed by the British Society for Antimicrobial Chemotherapy, the Infectious Diseases Society of America, or the Paul-Ehrlich-Society. They also stated that future studies should evaluate surgical procedures and compare different antimicrobial drugs using blinding.

Bibliographic details

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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.