Shorter courses of parenteral antibiotic therapy do not appear to influence response rates for children with acute hematogenous osteomyelitis: a systematic review

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Authors' objectives
To determine whether short courses (less than 1 week) of parenteral antimicrobial therapy show equivalent cure rates, compared with longer courses (greater than 1 week), in children with acute haematogenous osteomyelitis (AHO) caused primarily by Staphylococcus aureus.

Searching
MEDLINE and EMBASE were searched from January 1966 to April 2001. The Cochrane Controlled Trials Register, in the Cochrane Library, was searched from 1981 to July 2000. There were no restrictions on language or publication status. Over the course of the review, the search was periodically re-run in MEDLINE.

Study selection
Study designs of evaluations included in the review
To be included, the studies had to be prospective. Of the included studies, all were uncontrolled, except for one randomised controlled trial.

Specific interventions included in the review
Studies were included in the review if they identified the antimicrobial and its route (parenteral or oral) and duration of therapy. Specific antimicrobials included: cephradine, ampicillin, methicillin, cefazolin, oxacillin, clindamycin, nafcillin, cloxacillin, imipenem plus cilastatin, cephalothin, cephalaxin, penicillin V, dicloxacillin, flucloxacillin, cefaclor, bacampicillin, and cefadroxil.

Participants included in the review
Studies were included if they involved children aged between 3 months and 16 years, with AHO defined as: positive culture of Staphylococcus aureus from bone or periotem; or clinical signs of osteomyelitis and concurrent positive blood culture; or clinical signs and a compatible radiological study (nuclear scan or radiography). The clinical signs were to include swelling, warmth, tenderness and decreased ability to bear weight.

Outcomes assessed in the review
Studies were included if the outcome after an average of 6 months of follow-up was stated or could be inferred as clinical cure, failure or relapse.

How were decisions on the relevance of primary studies made?
Two authors independently selected studies for inclusion in the review. Open consensus was used to settle any differences.

Assessment of study quality
The authors do not report a method for assessing validity. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the assessment.

Data extraction
Two reviewers independently extracted the data from the included studies, with any disagreements resolved by consensus. Data were extracted on: study details, design (e.g. cohort), population (e.g. diagnosis), intervention (e.g. type of antibiotic and duration of treatment) and primary outcome (e.g. response rates).
Methods of synthesis

How were the studies combined?
Seven days or less of parenteral therapy was considered short course. As the cure rates were likely to be close to or exactly 100%, Wilson score confidence intervals were calculated (reference cited in review) rather than using normal theory-based confidence intervals (CIs). Under the hypothesis of homogeneity of the cure rates across cohorts, a fixed-effect estimate of the overall cure rate was provided by the total number of cured patients divided by the total number of patients. The same estimate was provided by an intercept-only logistic regression model.

Cohorts with different treatments within the same study were analysed as separate parallel groups. The difference between the overall cure rate under short- and long-term parenteral antimicrobial therapy was assessed using a z-test. A subgroup analysis comparing the overall cure rates for beta-lactams and macrolides was carried out using the same methods. The difference in the mean length of oral therapy for cohorts that had short- and long-term parenteral antimicrobial therapy was assessed using a t-test.

How were differences between studies investigated?
To test the homogeneity of the cure rates, the residual deviance from the logistic regression model was compared with a chi-squared distribution; the degrees of freedom were given by the number of cohorts minus one.

Results of the review
Eleven prospective studies providing 12 cohorts (n=230) were included in the review.

The duration of parenteral antimicrobial therapy ranged from 3 to 28 days.

The 7 cohorts that had less than 7 days of intravenous therapy (n=146) had a pooled cure rate of 95.2% (95% CI: 90.4, 97.7). There was no significant heterogeneity among their cure rates (chi-squared 8.2, d.f.=6, p=0.224).

The 5 cohorts that had a duration of intravenous therapy for 7 days or longer (n=84) had a pooled cure rate of 98.8% (95% CI: 93.6, 99.8). There was no significant heterogeneity among these cure rates (chi-squared 3.1, d.f.=4, p=0.537).

When pooling all of the cohorts, regardless of the duration of intravenous therapy, there was no significant heterogeneity among the cure rates (chi-squared 13.7, d.f.=11, p=0.248). The fixed-effect model gave a pooled cure rate of 96.5% (95% CI: 93.3, 98.2). There was no significant difference in the cure rate between the two groups (z-test p-value 0.838).

When comparing beta-lactams and macrolides there was no significant heterogeneity within either group (Beta-lactams: chi-squared 7.3, d.f.=7f, p=0.394. Macrolides: chi-squared 5.2, d.f.=4, p=0.159). The pooled cure rate for beta-lactams was 95.4% (95% CI: 90.3, 97.9) under a fixed-effect model. The pooled cure rate for macrolides was 98.0% (95% CI: 93.0, 99.4). There was no significant difference in the cure rate between the two groups (z-test p-value 0.286).

The duration of oral therapy in the short-term therapy group ranged from 15 to 39 days (mean: 32). For cohorts with a longer duration of intravenous therapy, the duration of oral therapy ranged from 18 to 56 days (mean: 33). There was no significant differences in the duration of oral therapy between the two groups.

Authors' conclusions
The results indicate that the cure rates are similar whether children with AHO are treated for a shorter or longer time period. Given the potential increased morbidity and cost associated with longer courses of intravenous therapy, this finding should be confirmed through a randomised equivalence trial.

CRD commentary
This review used appropriate inclusion criteria to select studies identified from searches of the Cochrane Controlled Trials Register and periodic searches of MEDLINE. Two reviewers were involved in selecting and extracting the primary studies, which may have helped limit bias in the review process. The authors investigated heterogeneity amongst the selected cohorts and appeared to combine these using appropriate techniques. The comparison of short-
and long-term courses was based on indirect comparisons of data taken mostly from uncontrolled studies. Therefore, the findings may not be reliable. The authors' decision not to quality assess the trials appears valid, as most of them were uncontrolled. However, the inherent low quality of such studies should have been emphasised in the review. Nevertheless, the authors' conclusions and recommendations appear to follow from the evidence presented.

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

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

Research: The authors recommend that serious consideration be given to conducting a randomised controlled trial. They stated 'Such a study could be developed to demonstrate equivalence between two durations of antibiotic therapy: a shorter course (i.e., 3-5 days) compared to a more “standard” course of 14 to 21 days. This would only be relevant if cure rates were not equivalent. The results from such a study could be used to better inform clinicians as to the management of children with AHO in the future'.

**Bibliographic details**


**Original Paper URL**

http://www.biomedcentral.com/1471-2334/2/16

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Acute Disease; Anti-Bacterial Agents /therapeutic use /administration & dosage; Cohort Studies; Infusions, Parenteral /methods; Osteomyelitis /etiology /drug therapy; Prospective Studies; Randomized Controlled Trials as Topic; Staphylococcal Infections /drug therapy /complications; Staphylococcus aureus /isolation & purification /drug effects; Treatment Outcome

**AccessionNumber**

12002008593

**Date bibliographic record published**

30/09/2003

**Date abstract record published**

30/09/2003

**Record Status**

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