Treatment of acute otitis media with a shortened course of antibiotics: a meta-analysis

Authors' objectives
To conduct a meta-analysis of randomised controlled trials of antibiotic treatment of acute otitis media (AOM) in children to determine whether outcomes are comparable in children treated with antibiotics for less than 7 days or at least 7 days or more.

Searching
MEDLINE (JANUARY 1966 TO July 1997), EMBASE (January 1974 to July 1997), Current Contents (January to July 1997), and Science Citation Index were searched. There were no language restrictions. In MEDLINE, search terms employed were "otitis media" in medical subject headings, modified by "acute" in the title or abstract. These terms were combined with the terms of randomised controlled trials, random allocation, double-blind method, single-blind method, or with the term randomised controlled trial in publication type. This strategy was approximated for the EMBASE search. Reference lists of relevant publications were reviewed to identify further trials. Where abstracts were referenced, attempts were made to obtain the published version.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with randomisation to less than 7 days of antibiotic treatment vs 7 days or more of antibiotic treatment.

Length of treatment ranged from one dose, to three days of treatment. Follow-up was 31 days for the primary outcome of treatment failure. The cumulative number of treatment failures, relapses and recurrences were reported from time of diagnosis until a final evaluation point between 1 to 3 months.

Specific interventions included in the review
Antibiotics used in the short course were:
1. Short-acting oral antibiotics: penicillin V potassium, amoxillin (-clavulanate), cefacior, cefixime, cefuroxime, cefpodoxime proxetil, and cefprozil.
2. Intramuscular ceftriaxone sodium.
3. Oral azithromycin.

Participants included in the review
Patients aged between 4 weeks and 18 years with a clinical diagnosis of AOM and no anti-microbial therapy at time of diagnosis were included.

Outcomes assessed in the review
The primary outcome of interest was treatment failure, which included lack of clinical resolution or relapse or recurrence of AOM, during a 31-day period following the initiation of therapy. Clinical resolution meant that the presenting signs or symptoms of AOM had improved or resolved. A secondary outcome was the cumulative number of treatment failures, relapses, and recurrences reported from time of diagnosis until a final evaluation point between 1 to 3 months. Middle ear effusion was not classified as treatment failure because of its documented persistence during the course of the disease, regardless of the treatment.

How were decisions on the relevance of primary studies made?
Clinical trials were independently assessed by the 7 authors according to 4 inclusion criteria. Inter-rater agreement on trial inclusion was assessed by the K statistic and agreement was categorised using the Landis and Koch guidelines.
Assessment of study quality
The internal validity of included trials was assessed using the Jadad scale. The scale assigned scores from 0 to 5 (best quality trial) based on the following criteria:

1. Study participants were randomly allocated to treatment using an appropriate method such as a random numbers table.
2. The intervention was double blinded using an identical looking and tasting placebo.
3. An accounting and description of study withdrawals were done. Concealment of treatment allocation was also evaluated for adequacy.

Validity was assessed independently by 7 authors. Rater assessment was blinded in the majority of trials by removing all identifying features of the published trial, such as author names, affiliations, and sources of financial support and by random ordering of trials. Interrater agreement on the quality score was assessed by the K statistic and agreement was categorised using the Landis and Koch guidelines.

Data extraction
Two authors independently abstracted primary and secondary outcome data from each blinded trial, using a standardised data extraction form. Where possible, outcome data were extracted for children both older and younger than 2 years, and for children with perforated and nonperforated tympanic membranes.

The number of withdrawals in each treatment arm, including those lost to follow-up, those with adverse drug effects, and those not complying with the study protocol, was recorded.

Methods of synthesis
How were the studies combined?
The meta-analyses were carried out using the Cochrane Collaboration's Revman 3.0 program. An odds ratio greater than one indicated a greater number of failures with the short course of antibiotics and superiority of the long course of antibiotics. The odds ratios (ORs) were calculated for individual trial outcomes and, using the Peto fixed-effect model, a summary OR was determined for trials pooled by antibiotic type. In addition, summary ORs were calculated using the DerSimonian and Laird random-effects model. To provide additional clinical meaning, results were also expressed as a summary risk difference in the failure rate and the number needed to treat to experience an additional failure in the short treatment arm.

How were differences between studies investigated?
Statistical heterogeneity among trials was assessed and trials with outlying ORs were further investigated.

Meta-analyses were performed on trials grouped by the pharmacokinetic behaviour of the antibiotic used in the short-treatment arm, as follows:

1. Short-acting oral antibiotics.
2. Oral azithromycin.
3. Intramuscular ceftriaxone.

Additional meta-analyses were conducted in the short-acting antibiotic group for treatment duration of 48 hours or less and greater than 48 hours.

Sensitivity analyses were conducted to assess the robustness of the meta-analysis by comparing summary ORs among groups redefined by:
1. Excluding trials of lower methodological quality (quality less than or equal to 2),

2. Excluding trials that included children with recurrent or chronic OM.

3. Excluding trials of comparisons between different antibiotics.

A sensitivity analysis of outcome criteria was also conducted by redefining clinical resolution to include cure, but not improved symptoms.

**Results of the review**

Thirty trials were included in the review, comprising 8215 participants. Fifteen trials used short-acting oral antibiotics, 4 used intramuscular ceftriaxone sodium, and 11 used oral azithromycin.

**Short-acting antibiotics given for 48 hours or less:** The summary OR for failures at one month or less in two trials that compared 48 hours or less of antibiotic treatment with at least 7 days gave was 2.99 (95% CI: 1.04, 8.54).

**Short-acting antibiotics given for more than 48 hours:** Twelve trials that reported outcomes at one month or less showed that the summary OR for treatment failure in children treated for 5 days, in comparison to children treated for 8 to 10 days, was 1.38 (95% CI: 1.15, 1.66). Treatment failure at an earlier evaluation point (8 to 19 days) in the 5-day treatment arm was more likely (1.52, 95% CI: 1.17, 1.98). The weighted mean failure rate was 19% (SE 7.6%) with 5 days of treatment and 13.7% (SE 6.4%) in the long treatment arm. The weighted summary risk difference was 7.8% (95% CI: 4%, 11.6%).

Among children treated with an antibiotic for 5 days and children treated for 8 to 10 days, primary outcomes at 20 to 30 days were not significantly different between the two groups (OR: 1.22; 95% CI: 0.98, 1.54). The weighted mean failure rate at 20 to 30 days was 15.7% (SE, 13.3%) with 5 days of treatment and 12.5% (SE, 12.4%) in the long treatment arm. The weighted summary risk difference was 2.3% (95% CI: -0.2%, 4.9%). This risk difference suggests that 44 children would need to be treated with the long course of short-acting antibiotics to avoid 1 treatment failure.

The summary OR for antibiotic failure at 30 days or less in children younger than 2 years and those who were at least 2 years old was 0.71 (95% CI: 0.3, 1.64) and 1.01 (95% CI: 0.53, 1.94), respectively.

**Outcome of ceftriaxone in the short-treatment arm:** The outcomes of treatment with ceftriaxone for 1 month or less and for 3 months or less were not significantly different from those of treatment with a longer course of oral antibiotics, with summary ORs of 1.25 (95% CI: 0.90, 1.72) and of 0.91 (95% CI: 0.57, 1.47) respectively.

**Outcome of azithromycin in the short-treatment arm:** The summary OR for primary outcomes following 3 or 5 days of treatment with azithromycin in comparison with another antibiotic was 1.09 (95% CI: 0.86, 1.38). The summary ORs did not change when children were treated for 3 days only, when children were evaluated at 10 to 14 days, or when children were evaluated at 30 days. The odds of treatment failure with azithromycin was 1.92 (95% CI: 0.73, 5.04) in children younger than 2 years and 1.34 (95% CI: 0.61, 2.94) in older children.

**Sensitivity analysis and publication bias:** Treatment failures at 30 days or less were not significantly more likely in the short than long treatment arm among short-acting antibiotic trials grouped as:

1. High quality trials.
2. Trials with adequate treatment allocation.
3. Trials that excluded children with current or chronic OM.

The majority of summary ORs for primary outcomes at 20 to 30 days did not change during any of the sensitivity analyses.

A funnel plot showed no evidence of a publication bias in the meta-analysis trials.
Adverse effects: The summary OR for gastrointestinal side effects in the short-acting antibiotics trials was 0.54 (95% CI: 0.43, 0.66). An OR less than 1 was observed only in trials in which the short course of antibiotics trials was compared with a 10-day course of the standard formula of amoxicillin-clavulanate. Once these trials were excluded, there was no difference in the likelihood of gastrointestinal side effects following a short or long course of antibiotics (OR: 1.13; 95% CI: 0.81, 1.57). Children treated with azithromycin were also less likely to experience gastrointestinal side effects than children treated with a long course of antibiotics (OR: 0.26; 95% CI: 0.19, 0.37), which was most often amoxicillin-clavulanate.

Authors' conclusions
This meta-analysis suggests that 5 days of short-acting antibiotic use is effective treatment for uncomplicated acute otitis media in children. Treatment with a shortened course of antibiotics has the potential to greatly reduce antibiotic use in regions where 10 days of treatment is considered the standard, with anticipated cost savings, improved compliance, and decreased antibiotic resistance.

CRD commentary
The review focuses on a well defined question. Inclusion and exclusion criteria were appropriate. The validity of included studies was adequately assessed, and low quality trials were excluded in a sensitivity analysis. Sufficient details of the individual studies were presented. Studies were combined appropriately, although the results of the tests for heterogeneity were not reported.

A thorough search of published literature was performed, but no attempt was made to identify unpublished material. However, a funnel plot suggested that a publication bias was not present.

This is a very thorough review and the conclusions follow from the results.

Implications of the review for practice and research
Practice: The authors state that their findings can be safely applied to children who present to ambulatory care settings with uncomplicated AOM, with some noteworthy exceptions. These findings do not apply to children with underlying disease and potentially children with recurrent or chronic OM.

Research: The authors state that future research could examine whether these findings can be extrapolated to other high risk children.

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