Antibiotics for acute otitis media: a meta-analysis with individual patient data

CRD summary
The review aimed to identify subgroups of children with acute otitis media (AOM) who would benefit from treatment with antibiotics. The authors concluded that antibiotics are beneficial in children younger than two years who have bilateral AOM, or AOM and otorrhoea, but an observational policy seems justified for most others. The first conclusion appears reliable, but the results do not directly support the second conclusion.

Authors’ objectives
To identify subgroups of children with acute otitis media (AOM) who would and would not benefit from treatment with antibiotics.

Searching
PubMed, EMBASE, the Cochrane Library and proceedings of international symposia on recent advances in otitis media were searched.

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

Specific interventions included in the review
Studies comparing treatment with antibiotics with placebo or no treatment were eligible for inclusion. The included studies compared children treated with amoxicillin, with or without clavulanate, versus placebo, or compared immediate administration of amoxicillin versus delayed treatment; the treatment courses were 7 or 10 days.

Participants included in the review
Studies that included children aged 0 to 12 years with AOM were eligible. The patients in the included studies were aged 6 months to either 2, 5, 10 or 12 years, or in one study were 3 to 10 years old; the mean age was 3.4 years. Approximately 50% of the children were male, and 50% had recurrent and 33% had bilateral AOM.

Outcomes assessed in the review
The studies had to report on pain and fever to be eligible. The assessment varied in the included studies (parent report, general practitioner assessment) and some studies also reported on other outcomes (e.g. otorrhoea, absence from school, analgesic consumption or adverse events). The primary outcome of the review was an extended course of AOM, defined as pain, fever (38 degrees C or higher) or both at 3 to 7 days. The secondary outcomes were fever at 3 to 7 days, pain at 3 to 7 days and adverse events.

How were decisions on the relevance of primary studies made?
The primary investigators of all selected trials were contacted and queried issues were resolved.

Assessment of study quality
The reviewers checked the obtained data for consistency, plausibility, integrity of randomisation and follow-up; some issues were queried and resolved through contact with the trial investigator or statistician. The reviewers assessed all trials regarding the use of proper randomisation methods, degree of follow-up, and blinding of the outcome assessor, patient and care giver.

Data extraction
The reviewers used the available data for outcomes and specified subgroups. Data were available for 90% (range: 81 to 98) of the outcomes and 72% (range: 28 to 100) of the subgroups. Missing data were estimated using multiple regression analyses within trials based on the correlation between individual variables with missing values and all other variables, as estimated from the complete data set. Fever and pain were extracted as dichotomous variables.

**Methods of synthesis**

How were the studies combined?
The authors calculated relative risks, rate differences (RDs) and the number-needed-to-treat (NNT) with 95% confidence intervals (CIs). A fixed-effect logistic regression analysis assessed whether the effect of antibiotics was modified by age, bilateral AOM, fever, otorrhoea, or a combination of these factors. The model adjusted for study and included interaction terms between antibiotic and each potential factor. If the interaction was statistically significant then results were presented for each subgroup. All analyses were performed on an intention-to-treat basis.

How were differences between studies investigated?
Heterogeneity between the studies was assessed using the I-squared statistic; as the resulting I-squared was lower than 25%, pooling of the studies was considered justified. For the five trials that used parental diaries, the percentage of children with an extended course during each consecutive day within each of the identified subgroups was calculated. Sensitivity analyses explored the results for trials that measured the outcomes on the same day, used the same dose regimen, or included placebo.

**Results of the review**
Six RCTs providing data from 1,643 individual patients were included. The data from four potentially relevant studies could not be obtained.

The quality of the included trials was generally high: five used adequate allocation concealment and outcome assessments, and loss to follow-up was less than 10%.

The overall relative risk of an extended course of AOM was 0.83 (95% CI: 0.78, 0.89) in favour of antibiotic treatment; the RD was 13% (95% CI: 9, 17) and the NNT was 8 children.

The effect of antibiotics on pain, fever, or both at 3 to 7 days varied by bilateral AOM (p=0.021), age and bilateral AOM (p=0.022), and otorrhoea (p=0.039). There were no significant differences for age alone. In children younger than two years of age with bilateral AOM, 30% of children on antibiotics and 55% of the controls still had pain and/or fever at 3 to 7 days; this corresponded to an RD of -25% (95% CI: -36, -14) and the NNT was 4. For children with otorrhoea, 24% of those on antibiotics and 60% of the controls had pain and/or fever at 3 to 7 days (RD -36%, 95% CI: -53, -19; NNT 3). Similar results by age and bilateral AOM were seen for pain alone at 3 to 7 days.

The most common adverse effect was diarrhoea, ranging from 4 to 21% in the treatment groups and from 2 to 14% in the control groups. One per cent to 8% of children in the antibiotic groups developed a rash compared with 2 to 6% in the control groups. No serious complications were mentioned.

Further analyses were reported in the paper.

**Authors’ conclusions**
Antibiotics seem to be most beneficial in relieving residual pain or fever at 3 to 7 days in children younger than two years of age with bilateral AOM, and in children with both AOM and otorrhoea. An observational policy seems justified for most other children with mild disease.

**CRD commentary**
The review stated a clear question and inclusion criteria. The search appeared thorough. Four of the 10 eligible trials could not be obtained, so it must be noted that the included studies represented a selection of a pool of relevant studies. There was no information on whether more than one reviewer selected, extracted and quality assessed the included
studies to reduce errors and bias. The data seemed to have been reanalysed thoroughly and queries were resolved with the help of the original trial investigators. Since approximately 10% of the outcome and 28% of the subgroup data were missing, these were estimated from the available data; this may increase the risk of error. The first sentence of the conclusion is reliable and follows directly from the data. However, the second statement is not directly supported by the results as, although the review showed significant differences between some subgroups, positive effects of antibiotics were seen in all subgroups so the conclusion about an observational policy may instead follow from other clinical considerations.

Implications of the review for practice and research
Practice: The authors stated that an observational policy seems justified for most other children with mild disease (i.e. apart from those younger than two years of age with bilateral AOM and those with AOM and otorrhoea).

Research: The authors stated no direct implications for research. However, they noted that their review did not cover other subgroups who may benefit more from antibiotic treatment, such as children with Down's syndrome or cleft palate, but there was no evidence from RCTs.

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