Evidence assessment of management of acute otitis media - I. The role of antibiotics in treatment of uncomplicated acute otitis media

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Authors' objectives
To synthesise the literature on the natural history of acute otitis media (AOM), the effectiveness of antibiotic treatment in uncomplicated AOM, and the relative effectiveness of specific antibiotic regimens.

Searching
The following sources were searched: MEDLINE from 1966 to March 1999; the Cochrane Library (to March 1999); HealthSTAR from 1975 to March 1999; International Pharmaceutical Abstracts from 1970 to March 1999; CINAHL from 1982 to March 1999; BIOSIS Previews from 1970 to March 1999; and EMBASE from 1980 to March 1999. Grey literature was identified by reviewing abstracts, reference lists in proceedings, and published articles. The search terms used were a combination of three modules: the first used an explosion of the term 'OM' (otitis media); the second used an explosion of 'OM' as textwords; the third used an explosion of the MeSH term for anti-infective agents. Further details of the search terms were provided in the paper. Articles in any language were considered.

Study selection
Study designs of evaluations included in the review
Both randomised controlled trials (RCTs) and cohort studies were accepted for the key question on natural history, whereas only RCTs were accepted for the key questions on antibiotic effectiveness. Case reports, editorial letters, reviews and practice guidelines were excluded.

Specific interventions included in the review
Antibiotic treatment including amoxicillin, penicillin, benthazine penicillin, amoxicillin-clavulanate, cefaclor, cefuroxime, cefpodoxime, cefprozil, cefitiben, ceftriaxone, and azithromycin. The doses were unclear from text.

Participants included in the review
The participants had to be children aged between 4 weeks and 18 years who were seeking treatment for uncomplicated AOM. Studies using patients with immunodeficiencies and craniofacial abnormalities, including cleft palate, were excluded.

Outcomes assessed in the review
The major outcomes included clinical signs and symptoms (e.g. clinical failure as defined by the individual studies, presence of pain or fever, or presence of middle ear effusion) and the presence or absence of adverse effects from antibiotic treatment.

How were decisions on the relevance of primary studies made?
Two physicians independently screened all the titles and abstracts for inclusion. Using the same patient and study criteria mentioned earlier, the two physicians re-screened each citation accepted using the contents of the full articles. Any discrepancies were resolved with the assistance of a senior investigator. A physician also reviewed the articles in non-English languages using the same inclusion-exclusion criteria, with the assistance of a translator. The non-English articles were not reviewed in duplicate. The studies were not masked at any stage.

Assessment of study quality
Validity was assessed using the scale of Jadad et al. (see Other Publications of Related Interest no.1), which is a validated tool that assesses randomisation, blinding and the reporting of participant withdrawal. Cohort studies were evaluated using eight criteria: the presence or absence of a clear definition of the study cohort; an early inception point; a clear pathway of patient entry; complete follow-up; a description of the drop-outs; objective outcome criteria; a blind outcome assessment; and adjustment for extraneous factors. The reviewers also evaluated the adequacy of the
definition of AOM in terms of middle-ear effusion, rapid onset, and signs and symptoms of AOM inflammation. Two physicians independently evaluated the quality of each study. Any discrepancies were resolved with the assistance of a senior investigator. There was no information about whether the physicians were blinded to the source.

**Data extraction**
The same physicians that evaluated the quality of the studies independently extracted information about the interventions, inclusion and exclusion criteria, participant age and otitis-prone status, sample sizes, outcome measures, and the results of each study.

**Methods of synthesis**
How were the studies combined?
All meta-analyses used the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2), which incorporates both within- and between-study heterogeneity. For the natural history question, the pooled random-effects incidence rates of the outcome measures were derived. The absolute rate difference of clinical failures between any two antibiotic regimens was used to evaluate their relative effectiveness. The effectiveness of individual antibiotics, rather than antibiotics as a class, was assessed because it would be more relevant to actual practice. The only a priori exception made was to group ampicillin and amoxicillin because of their great similarity. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
The authors state that heterogeneity between the studies was investigated, but do not report a formal method of assessment. The studies were grouped according to which treatments were compared.

**Results of the review**
A total of 80 studies (74 RCTs and 6 cohort studies) met the inclusion criteria. There were 15 studies for the natural history question; 9 RCTs for the antibiotic versus non-antibiotic question; 34 studies of amoxicillin or trimethoprim-sulfamethoxazole versus other antibiotics; one study of amoxicillin, twice daily versus three times a day; one study of high- versus standard-dose amoxicillin; and 35 studies of short- versus long-term antibiotic therapy.

Overall, children with AOM not treated with antibiotics experienced a 1- to 7-day clinical failure rate of 19% (95% confidence interval, CI: 0.10, 0.20) and few suppurative complications. When patients were treated with amoxicillin, the 2- to 7-day clinical failure rate was reduced to 7%, a 12% (95% CI: 0.04, 0.20) reduction. Adverse events, primarily gastrointestinal, were more common among children on cefixime than among those on ampicillin or amoxicillin. They were also more common among children on amoxicillin-clavulanate than among those on azithromycin.

**Authors’ conclusions**
The majority of uncomplicated cases of AOM resolve spontaneously without apparent suppurative complications. Ampicillin or amoxicillin confer a limited therapeutic benefit. There was no evidence to support any particular antibiotic regimens as more effective at relieving symptoms. Certain antibiotics are more likely than others to cause diarrhoea and other adverse events.

**CRD commentary**
This was a thorough review that adhered to a robust methodology, e.g. a thorough literature search, independent assessors, and a quality assessment of the included studies.

The conclusions follow from the results but, as noted by the authors, the results should be interpreted with caution given the poor available evidence.
Implications of the review for practice and research

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

Research: The authors state that bacterial antibiotic resistance should be addressed in future studies, both as a factor influencing AOM outcome and as an outcome of antibiotic use in AOM.

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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.