Systematic review of topical antimicrobial therapy for acute otitis externa

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CRD summary
The authors concluded that topical antimicrobial treatment was very effective for acute otitis externa, although there was little difference between different antimicrobials. Their conclusions about the effectiveness of antimicrobials versus placebo are likely to be reliable, but few studies compared the same treatments and this limited comparisons between antimicrobials.

Authors' objectives
To evaluate the efficacy of topical antimicrobials for acute otitis externa (AOE).

Searching
MEDLINE, CINAHL (inception to July 2005) and the Cochrane Controlled Trials Register were searched using the reported search terms. Articles in Spanish, Italian, Russian and Danish were translated.

Study selection
Study designs of evaluations included in the review
Parallel-group randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that evaluated topical therapy and compared any of the following medications were eligible for inclusion: antimicrobial versus placebo; antiseptic versus antimicrobial; quinolone antibiotic versus non-quinolone antibiotic; steroid-antimicrobial combination versus antimicrobial alone; and antimicrobial-steroid combination versus steroid alone. Details of the specific medications used in the included studies were reported. A minority of studies explicitly reported the use of aural toilet. In 3 studies, wicks were used. In all but one study, therapy was administered for at least 7 days; most studies advised therapy for between 7 and 11 days.

Participants included in the review
Studies of patients with diffuse AOE were eligible for inclusion. Studies of patients with otorrhoea caused by conditions other than diffuse AOE were excluded. Most of the included studies involved adults and children; none involved only children. Where relevant, the minimum age of children ranged from 1 to more than 6 years. In most studies (55%), patients with perforation of the tympanic membrane were excluded. About half of the studies did not explicitly define AOE.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The review assessed clinical cure, clinical improvement, bacteriological cure and adverse events. Clinical cure was defined as the absence of all presenting signs and symptoms of diffuse AOE, whereas clinical improvement was defined as partial or complete relief of presenting signs and symptoms. Clinical outcomes were assessed at several time points: early (days 3 to 4), end-of-therapy (7 to 13 days) and test-of-cure (14 to 21 days).

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the identified studies.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and adequacy of randomisation, blinding and the handling of withdrawals. The maximum possible score was 5 points. The authors did not state how the validity assessment was performed.
Data extraction
Two reviewers independently extracted the data using a standardised form. Binary outcomes data of interest were preferred but continuous outcomes data were also extracted. For studies with more than two treatment groups, data from the two most relevant groups were used. The data were extracted on a per-protocol basis because most studies did not report intention-to-treat data. Any disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
How were the studies combined?
Studies that provided sufficient data were combined using random-effects meta-analysis. Pooled absolute rate differences (RDs) and 95% confidence intervals (CIs) were calculated where two or more studies assessed clinical cure, bacteriological cure or adverse events at the same time point. In most of the studies included in the meta-analyses, the unit of analysis was patients; 2 studies that used ears as the unit of analysis were also included on the grounds that over 90% of patients had unilateral AOE.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. For some meta-analyses, the influence of industry funding, study quality, meta-analysis model (fixed-effect and random-effects), reporting of aural toilet, and individual studies was discussed in the text.

Results of the review
Twenty RCTs (n=3,289) were included in the review and 18 RCTs (n=3,159) were included in the meta-analyses.

The Jadad scores ranged from 1 to 5 (median 2). Only 2 studies scored the maximum of 5 points.

Compared with placebo, antimicrobials (neomycin/methylprednisolone and acetic acid/glyceryl triacetate) were associated with a significant increase in clinical cure rate at 3 to 10 days (RD 0.46, 95% CI: 0.29, 0.63, p<0.001; 2 RCTs, n=89) and bacteriological cure rate (RD 0.61, 95% CI: 0.46, 0.76, p<0.001; 2 RCTs, n=112). No statistically significant heterogeneity was detected (I-squared 0 for both meta-analyses). The studies were conducted by the same authors and were of high quality (both Jadad scores were 4 and both studies were double-blinded).

Compared with steroid alone (betamethasone and hydrocortisone butyrate), steroid-antibiotic combinations (oxytetracycline/polymyxin B/hydrocortisone) were associated with a significant decrease in clinical cure rate at 7 to 11 days (RD -0.20, 95% CI: -0.38, -0.03, p=0.021; 2 RCTs, n=92).

Quinolone antibiotics (ofloxacin, ciprofloxacin with and without dexamethasone or hydrocortisone) were associated with a significant increase in bacteriological cure rate compared with nonquinolone antibiotics (gentamicin, tobramycin, polymyxin/hydrocortisone plus neomycin and oxytetracycline), (RD 0.08, 95% CI: 0.006, 0.16, p=0.035; 6 RCTs, n=980). Significant heterogeneity was found (I-squared 74%). The difference between treatments was no longer significant after the exclusion of one small study with an RD at least twice that of the other studies, but heterogeneity remained significant (p=0.021). There were no significant differences in clinical cure rates and adverse events between quinolone antibiotics and nonquinolone antibiotics, based on analyses of between 476 and 1475 patients from between 2 and 6 studies. Significant heterogeneity was found in most of these analyses.

There were no significant differences between antiseptic versus antimicrobial treatments and steroid-antimicrobial combinations versus antimicrobial alone.

Authors' conclusions
Topical antimicrobial treatment was very effective for AOE but there was little difference between different topical antimicrobial agents.
CRD commentary

The review question was clear in terms of the study design, participants and intervention. The outcomes assessed in the review were stated clearly. Three relevant sources were searched and attempts were made to minimise language bias. However, only limited attempts were made to locate unpublished studies, which raises the possibility of publication bias and missing studies. Methods were used to minimise reviewer errors and bias in the study selection and data extraction processes, but it was unclear whether similar steps were taken in the assessment of validity. Study quality was assessed using specified criteria and the results were reported.

Only studies reporting specific outcomes at the same time were pooled using meta-analysis. Comparisons between studies were generally clinically heterogeneous with respect to the medications used. Statistical heterogeneity was assessed and, where significant heterogeneity was found, some potential sources were investigated. The authors’ conclusions regarding the effectiveness of antimicrobials versus placebo are likely to be reliable, but studies comparing different classes of treatment were clinically and statistically heterogeneous and the finding of no difference between treatments may not be reliable.

One of the authors was a prior consultant for Alcon and Daiichi Pharmaceuticals.

Implications of the review for practice and research

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

Research: The authors stated the need for further well-conducted and reported RCTs to compare different treatments for AOE and to confirm the review findings of a benefit for steroid alone versus steroid-antibiotic combinations and quinolones versus nonquinolones.

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the reliability of the review and the conclusions drawn.