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Interventions for acute otitis externa (Review)

Kaushik V, Malik T, Saeed SR

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[Intervention Review]

Interventions for acute otitis externa

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ABSTRACT

Background

Acute otitis externa is an inflammatory condition of the ear canal, with or without infection. Symptoms include ear discomfort, itchiness, discharge and impaired hearing. It is also known as 'swimmer's ear' and can usually be treated successfully with a course of ear drops.

Objectives

To assess the effectiveness of interventions for acute otitis externa.

Search methods

Our search for published and unpublished trials included the Cochrane Ear, Nose and Throat Disorders Group Trials Register; CENTRAL; PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources. The date of the most recent search was 6 January 2009.

Selection criteria

Randomised controlled trials evaluating ear cleaning, topical medication or systemic therapy in the treatment of acute otitis externa were eligible.

We excluded complicated acute otitis externa; otitis externa secondary to otitis media or chronic suppurative otitis media; chronic otitis externa; fungal otitis externa (otomycosis); eczematous otitis externa; viral otitis externa and furunculosis.

Data collection and analysis

Two authors assessed eligibility and quality.

Main results

Nineteen randomised controlled trials with a total of 3382 participants were included. Three meta-analyses were possible. The overall quality of studies was low.

Topical antimicrobials containing steroids were significantly more effective than placebo drops: OR 11 (95% CI 2.00 to 60.57; one trial).

In general, no clinically meaningful differences were noted in clinical cure rates between the various topical interventions reviewed. One notable exception involved a trial of high quality which showed that acetic acid was significantly less effective when compared with

antibiotic/steroid drops in terms of cure rate at two and three weeks (OR 0.29 (95% CI 0.13 to 0.62) and OR 0.25 (95% CI 0.11 to 0.58) respectively).

One trial of low quality comparing quinolone with non-quinolone antibiotics did not find any difference in clinical cure rate.

No trials evaluated the effectiveness of ear cleaning.

Only two trials evaluated steroid-only drops. One trial of low quality suggested no significant difference between steroid and antibiotic/steroid but did not report the magnitude or precision of the result. Another trial of moderate quality comparing an oral antihistamine with topical steroid against topical steroid alone found that cure rates in both groups were high and comparable (100% (15/15) and 94% (14/15) respectively at three weeks).

Authors' conclusions

There is a paucity of high quality trials evaluating interventions for acute otitis externa. The results of this systematic review are largely based on odds ratios calculated from single trials, most of which have very broad 95% confidence intervals because of small to modest sample sizes. The findings may not be wholly generalisable to primary care for a variety of reasons; only two of the 19 trials included in the review were conducted in a primary care population setting, and in 11 of the 19 trials ear cleaning formed part of the treatment (an intervention unlikely to be available in primary care). Despite these reservations, some meaningful conclusions can be drawn from the evidence available:

Topical treatments alone, as distinct from systemic ones, are effective for uncomplicated acute otitis externa. In most cases the choice of topical intervention does not appear to influence the therapeutic outcome significantly. Any observed differences in efficacy were usually minor and not consistently present at each follow-up visit. Acetic acid was effective and comparable to antibiotic/steroid at week 1. However, when treatment needed to be extended beyond this point it was less effective. In addition, patient symptoms lasted two days longer in the acetic acid group compared to antibiotic/steroid.

The evidence for steroid-only drops is very limited and as yet not robust enough to allow us to reach a conclusion or provide recommendations. Further investigation is needed.

Given that most topical treatments are equally effective, it would appear that in most cases the preferred choice of topical treatment may be determined by other factors, such as risk of ototoxicity, risk of contact sensitivity, risk of developing resistance, availability, cost and dosing schedule. Factors such as speed of healing and pain relief are yet to be determined for many topical treatments and may also influence this decision.

Patients prescribed antibiotic/steroid drops can expect their symptoms to last for approximately six days after treatment has begun. Although patients are usually treated with topical medication for seven to 10 days it is apparent that this will undertreat some patients and overtreat others. It may be more useful when prescribing ear drops to instruct patients to use them for at least a week. If they have symptoms beyond the first week they should continue the drops until their symptoms resolve (and possibly for a few days after), for a maximum of a further seven days. Patients with persisting symptoms beyond two weeks should be considered treatment failures and alternative management initiated.

PLAIN LANGUAGE SUMMARY

Interventions to treat acute otitis externa, a specific form of ear canal inflammation also known as swimmer's ear

Acute otitis externa causes inflammation of the ear canal. It is a common clinical problem encountered in general practice. This review assesses the various forms of medication used to treat the condition. Nineteen randomised controlled trials were included (3382 participants). Most were of low quality. The findings of the review may not be wholly relevant to primary care as most of the trials were conducted in a hospital setting and over half involved ear cleaning as part of the treatment (this is generally not available in primary care). However, the review does demonstrate that topical treatments alone are effective at treating acute otitis externa. There was little to choose between them in terms of effectiveness. However, when treatment needs to be extended beyond one week acetic acid drops appear to be less effective than antibiotic/steroid drops. In addition, symptoms persist for two days longer in those treated with acetic acid. More research is needed to determine the effectiveness of steroid-only drops. Patients treated with antibiotic/steroid drops can expect their symptoms to last for approximately six days after treatment has begun.

BACKGROUND

Definition

Otitis externa is a broad term used to describe an inflammatory condition affecting the ear canal, with or without infection. The inflammation is usually generalised throughout the ear canal and can affect the outer ear. It can be subdivided into acute (less than six weeks), recurrent acute and chronic (more than three months). Acute otitis externa is the most common form occurring in everyday practice (Boustred 1999), and will form the focus of this review. There are a number of popular synonyms such as 'hot weather ear', 'tropical ear' and 'swimmer's ear'.

Symptoms

Acute otitis externa typically presents with discomfort within the ear canal which is worsened if the outer ear is touched or pulled gently. The affected ear can feel blocked or full. Discharge from the ear canal can occur. If the ear canal becomes very swollen the patient may also complain of hearing loss.

Frequency

Each year otitis externa is reported to affect four out of 1000 Americans (Guthrie 1999), and has a 12-month prevalence in the UK of just over 1% (Rowlands 2001). In the Netherlands the incidence is 12 to 14 per 1000 population per year (Rooijackers-Lemmens 1995).

There is an increase in episodes observed at the end of summer. However, it is not clear whether this is due to warmer ambient temperature, increased humidity, increased exposure to water or patients delaying consultation because they were on holiday (Rowlands 2001).

Demographics

Acute otitis externa is seen in all age groups. The peak incidence in one study was in children aged seven to 12 years (Roland 2002). It affects males and females equally and is five times more common in regular swimmers compared to non-swimmers (Hoadley 1975).

Impact on quality of life

In one study, otitis externa was found to be disabling enough to cause 36% (35/98) of patients to interrupt their daily activities for a median duration of four days, with 21% (21/98) requiring bed rest for a median period of three days (van Asperen 1995).

Predisposing factors

Acute otitis externa occurs following a disturbance in the normal protective acidic milieu within the ear canal, secondary to a complex interaction of environmental and host factors.

Environmental factors

Environmental factors comprise the following.

- Moisture - macerates the skin of the canal, elevates ear canal pH and removes the protective layer of cerumen (e.g. swimming, perspiration, high humidity).
- Trauma - leads to a breech in the integrity of the ear canal skin (e.g. cotton buds, fingernails, hearing aids, ear plugs, paper clips, match sticks, mechanical removal of cerumen).
- High environmental temperatures.

Host factors

Host factors are as follows.

- Anatomical – wax and debris accumulate and lead to moisture retention (e.g. a narrow ear canal, hairy ear canal).
- Cerumen - absence or overproduction of cerumen (leads to loss of the protective layer and moisture retention respectively).
- Chronic dermatological disease (e.g. atopic dermatitis, psoriasis, seborrhoeic dermatitis).
- Immunocompromise (e.g. chemotherapy, HIV, AIDS).

Complications

Regional dissemination of infection can lead to myringitis, auricular cellulitis, perichondritis, facial cellulitis and systemic toxicity. It may progress to chronic otitis externa and can lead to ear canal stenosis. Necrotising otitis externa is a life-threatening extension of otitis externa into the temporal bone resulting in osteomyelitis. It is caused almost exclusively by *Pseudomonas aeruginosa* and occurs most often in elderly patients with diabetes mellitus and in the immunocompromised.

Treatment

Most cases of acute otitis externa are treated in primary care by general practitioners or family practice physicians. In the UK only 3% of patients with otitis externa treated in primary care are referred to secondary care (Rowlands 2001).

The mainstays of treatment in primary care are the use of a topical antimicrobial (antiseptics or antibiotics, with or without steroids) and avoidance of precipitating factors. Management of pain is also required. Refractory cases of uncomplicated acute otitis externa referred to secondary care usually fall into two categories. Firstly, those with very swollen ear canals through which treatment cannot be administered. Insertion of a medicated wick will address this problem. Secondly, patients with copious amounts of debris and discharge within the canal. This responds well to ear cleaning (dry-mopping or suction) followed by a further course of topical therapy.

Topical antibiotics are generally recommended as the first-line treatment of choice (Hannley 2000). However, recent reviews have shown that up to 40% of patients are prescribed systemic medication in addition to topical therapy, many of which are not active against *Pseudomonas aeruginosa* or *Staphylococcus aureus* (the most common bacterial pathogens in otitis externa) (Halpern 1999; Rowlands 2001). Only part of that use will be explained by a concomitant diagnosis of otitis media or evidence of regional spread of otitis externa. The significant use of oral antibiotics, in addition to topical therapy, has implications in terms of cost, risk of side effects and increased likelihood of non-compliance. The emergence of bacterial resistance through over-zealous use of oral antibiotics is another major concern.

Topical antibiotics commonly contain an aminoglycoside (neomycin, gentamicin) or a fluoroquinolone (ciprofloxacin, ofloxacin). Topical aminoglycosides are potentially ototoxic when used in the presence of a perforated tympanic membrane, whereas topical fluoroquinolones are not. If the tympanic membrane is known to be intact and the middle ear and mastoid are closed, the use of a potentially ototoxic preparation presents no risk of ototoxic injury (Roland 2004b). Consequently, most cases of acute otitis externa can be treated with either a topical

aminoglycoside or a topical fluoroquinolone. The difficulty arises when the integrity of the tympanic membrane is not known (e.g. if the tympanic membrane is obscured by debris, discharge or swelling). If a tympanic membrane perforation was present but not visible, the use of an aminoglycoside drop would inadvertently put the patient at risk of developing ototoxicity. To date no specific guidance has been issued on this matter. However, cognizance of guidelines issued for treating middle ear disease would support the use of a topical antibiotic preparation free of potential ototoxicity when the integrity of the tympanic membrane was unknown. In the UK, non-ototoxic quinolone drops are not licensed for use in the ear. Individual doctors have the option of either using these drops 'off license' or a short course of aminoglycoside drops. Both practices have been deemed acceptable by ENT-UK (the national representative body for Ear, Nose and Throat surgeons in the UK) (Phillips 2007).

Neomycin is associated with a 15% incidence of contact dermatitis; the development of such contact sensitivity should be considered a possibility when patients with acute otitis externa fail to completely resolve with treatments containing it.

In recent years the possibility of significant bacterial resistance emerging following the use of topical ear medication has been raised. It was previously thought that a lack of significant systemic absorption and the ability of topical antibiotics to achieve very high concentrations in the middle ear would make this scenario very unlikely. However, evidence from the ophthalmology literature showing increasing bacterial resistance to topical fluoroquinolone, aminoglycoside and chloramphenicol drops used to treat corneal ulcers has raised concern (Brown 2007). A recent evidence-based review concluded, on the basis of the grade B evidence available, that no significant topical antibiotic resistance develops from the use of ototopical antibiotic treatment (Weber 2004). The question of whether ototopical medication can produce systemic resistance and, potentially, failure of systemic antibacterial therapy remains unanswered. In the future, it may be the case that antiseptics, used commonly in the past, could see a resurgence.

Microbiology

The microbiology of otitis externa varies according to geographical location. In general, the most common organisms reported in acute otitis externa are *Pseudomonas* and *Staphylococcus* species. Fungi are a less common cause (Roland 2002). Cases of acute otitis externa can usually be treated empirically without the need for prior microbiological culture. Ear swabs tend to be reserved for refractory cases. MRSA (methicillin-resistant *Staphylococcus aureus*) otitis externa is an emerging concern. Thus far it has been treated successfully with ear cleaning and topical treatment, although there remains an underlying concern that this may not be sufficient in the future (Walshe 2001).

Prevention

Prevention involves avoidance of predisposing factors and the treatment of any underlying dermatological condition. Any self-inflicted trauma to the ear canal should be eliminated. Frequent washing of the ears with soap should be avoided as the alkaline residue neutralises the acidic pH the ear canal. With regard to water, two options are available: the first is to observe strict water precautions (preventing water entering the ear canal) whilst bathing or swimming through the use of ear plugs (kept clean to prevent re-infection), a bathing cap, or application of cotton-balls smeared with petroleum jelly (Vaseline) to cover the ear canal entrances. The second option is ensure the ear canals are emptied of water after bathing or swimming, either by tilting the head and pulling on the ear to help empty it, or using a hair dryer on the lowest heat setting to dry the ears. It has been suggested that the instillation of acidifying drops after swimming or bathing will also help.

OBJECTIVES

To determine the effectiveness of different methods of treating acute otitis externa. Interventions considered include topical astringents, topical antiseptics, topical antibiotics, topical steroids, topical combination treatments, oral antibiotics and ear cleaning.

METHODS

Criteria for considering studies for this review

Types of studies

Double or single-blind randomised controlled trials (we excluded open/non-blinded trials).

Types of participants

Any participant (adult or child) with acute otitis externa with intact tympanic membranes. We excluded subjects with complicated acute otitis externa, chronic otitis externa, otitis externa secondary to otitis media or chronic suppurative otitis media, overt fungal otitis externa, eczematous otitis externa, viral otitis externa, furunculosis and necrotising otitis externa.

Types of interventions

1. Ear cleaning.
2. Topical treatments (astringents, antiseptics, antibiotics, steroids or combination treatments).
3. Oral antibiotics.

Ear cleaning includes dry mopping, syringing or suctioning, with or without instillation of cleaning solutions.

Types of outcome measures

Primary outcomes

1. Resolution of symptoms (e.g. ear discomfort, discharge), however determined.
2. Resolution of signs (e.g. erythema, oedema), however determined.

Secondary outcomes

1. Eradication of pathogenic ear canal bacteria, determined by cultures.
2. The recurrence of symptoms, however determined.
3. Complications from treatment (e.g. sensitivity reactions).

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 6 January 2009.

Electronic searches

We searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 4, 2008); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; *m*RCT (Current Controlled Trials) and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. (Handbook 2008)). Search strategies for key databases including CENTRAL are shown in Appendix 1.

Searching other resources

Reference lists of identified studies were scanned for further trials. PubMed; TRIPdatabase; NHS Evidence - ENT & Audiology; and Google were also searched to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials.

Data collection and analysis

Eligibility assessment

Vivek Kaushik (VK) and Tass Malik (TM) independently reviewed the titles and abstracts identified by the search strategy to identify potentially relevant trials.

VK retrieved the full papers for all potentially relevant studies. VK and TM assessed their eligibility to be included in the review using an eligibility form based on the stated inclusion criteria. Multiple publications identified from the same data set were reported as one trial. Where outcomes were not reported, we contacted the author of the paper for this information as the data may have been collected but not reported. We excluded studies that did not meet the inclusion criteria for this review and stated the reason in the 'Characteristics of excluded studies' table.

Assessment of risk of bias

VK and TM assessed the methodological quality of all the trials identified as eligible for inclusion. Where necessary, we contacted the study authors for further clarification.

We assessed the methodological quality of trials in terms of generation of allocation sequence, allocation concealment, blinding and inclusion of randomised participants. We classified generation of allocation sequence, allocation concealment and the inclusion of randomised participants as adequate, inadequate and unclear as outlined by Juni 2001. Blinding was classified as double-blind or single-blind.

Data collection

VK extracted data on study characteristics, including methods, participants, interventions and outcomes, and recorded these on standard forms. In studies where data were insufficient or missing, we contacted the authors of the original studies. This was mainly done through electronic mail. If there was no reply on the first occasion, we made a second attempt.

Where possible we extracted data to allow an intention-to-treat analysis (i.e. the analysis should include all the participants in the groups to which they were originally assigned). If the number randomised and the numbers analysed were inconsistent, we calculated a percent loss to follow up and reported this information in additional Table 1. For binary outcomes, we recorded the total number of participants and number with the event in each group of the trial. For continuous outcomes, for each group, we extracted the number of participants, and the arithmetic means and standard deviations.

Data analysis

VK entered data into Review Manager 5.0 (RevMan 2008).

Pooling of data from individual studies was considered valid only if the drug categories being compared were the same and the time points at which data were collected were similar.

For binary data, we combined trials using odds ratios (OR) and 95% confidence intervals (CI). We combined trials with continuous data using weighted mean difference (WMD) and its 95% confidence interval. Where data were reported using medians and ranges, or there was evidence of skewed data, we reported medians and ranges where possible (dividing the mean by the standard deviation (SD); results of < 1.64 indicate a positive skew). If continuous data were reported using geometric means, we combined the findings on a log scale and reported on the original scale.

If a multiple-intervention trial had more than one intervention group in common in relation to a specific meta-analysis, these control groups were combined and compared to the experimental intervention group, thus creating a single pair-wise comparison. This avoids 'double-counting' participants in the 'shared' intervention group(s) which would create a unit of analysis error due to the unaddressed correlation between the estimated intervention effects from multiple comparisons.

Trialists would usually measure their outcome measures on more than one occasion. In general, these assessment visits fell into the following categories: early (e.g. half-way through treatment), end-of-therapy (a day or so after the cessation of treatment), test-of-cure (around a week after treatment), or test-of-recurrence (a few weeks after treatment had finished). Trialists varied in the number and timing of visits they chose. In order to make a fair comparison between trials it is important to compare outcome measures taken at similar times. It was therefore decided a priori that pooling of data from different studies (meta-analysis) would only be performed on outcome measures taken at similar times.

The primary analysis is of all eligible studies. If a sufficient number of trials is available for future updates (not available for each comparison in this version of the review), we will explore whether heterogeneity can be explained using subgroup analyses or meta-regression for the following factors: age (under 16, and adults 16 years or older), ear cleaning (dividing studies into those with some form of ear cleaning, and those without), co-interventions (dividing studies into those with treatment comparison alone, and those with treatment comparison in combination with other co-interventions), and methodological quality (initially excluding studies of poorest quality). Sensitivity analyses will also be used

to explore methodological quality (notably adequate concealment) and trial design (e.g. cluster randomisation). We will display the results for each sensitivity analysis according to the subgroups within each methods category.

The sensitivity analysis will include the following, as outlined in the statistical guidelines in the Cochrane Ear, Nose and Throat Group 'Guidelines for Reviewers' (Cochrane ENT Guideline updated November 2000).

1. Repeat the analysis excluding unpublished studies (if any).
2. Repeat the analysis excluding studies of the lowest quality (already done if there is heterogeneity).
3. If there are one or more very large studies, we will repeat the analysis excluding these, to investigate how much they dominate the results.

For this version of the review, we visually examined forest plots, in conjunction with the Chi^2 test, using a 5% level of statistical significance, and used the I^2 statistic. The I^2 statistic describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 30% is usually considered important (Deeks 2004). There were insufficient trials to investigate publication bias using funnel plots; this may be done in further updates of the review.

RESULTS

Description of studies

Search results

We reviewed full texts of 80 trials, and included 19 as eligible for this review - see breakdown of numbers below. Trials with duplicate publications were identified and referred to under the main trial publication. We attempted to include all relevant studies regardless of language.

- 80 trials: full texts obtained for eligibility assessment.
- 61 trials excluded: 55 English only and six were in non-English languages.
- 19 trials included (3382 randomised participants): 18 English only and one non-English language.

The 'Characteristics of excluded studies' table outlines the reasons for excluding studies following review of their full texts. The 'Characteristics of included studies' table provides information on the included trials; see also the following additional tables: Table 1 (Methodological quality of included studies); Table 2 (Bilateral disease: numbers for ears versus participants); Table 3 (Participant eligibility criteria, including acute otitis externa diagnostic criteria); Table 4 (Intervention regimens used); and Table 5 (Outcomes assessed).

Age, setting, location and sample size (for included studies)

See the 'Characteristics of included studies' table for details.

Age

Ages varied: nine trials included both children and adults, eight were in adults only, one was in children only and one trial did not specify explicitly. Details are reported in the 'Characteristics of included studies' table. When results were reported separately for adults and children they were combined for analytical purposes to provide consistency across studies.

Setting

Seventeen trials were based in specialist clinics. Two were based in primary care (Jones 1997; van Balen 2003).

Location

Locations were as follows: UK (four), USA (seven), Sweden (two), Germany (two), Netherlands (one), Austria (one), Argentina (one) and Spain (one).

Sample size

Sample size varied between studies and ranged from 28 to 601.

Diagnostic criteria for included participants

Additional Table 3 provides eligibility criteria and more detailed acute otitis externa diagnostic criteria.

The definitions of acute otitis externa used by trialists were not explicit, varied between studies and in some cases were not stated.

Trials specifically evaluating acute otitis externa were included in this review: Freedman 1978; Jones 1997; Masood 2008; Mosges 2007; Neher 2004; Olivera 2004; Roland 2004; Schwartz 2006; van Balen 2003; Wadsten 1985.

Trials referring to "otitis externa" were included if there was strong evidence to suggest they were studying acute otitis externa (Cannon 1967; Emgard 1999; Slack 1987; Tsikoudas 2002).

Trials involving cases of recurrent acute otitis externa were permitted.

Trials involving chronic otitis externa, eczematous otitis externa or fungal otitis externa were excluded.

The maximum duration of signs and symptoms was only mentioned in five studies and ranged from two to four weeks.

Inclusion criteria were typically brief.

Exclusion criteria varied from none to exhaustive.

Studies investigating otorrhoea, mastoid cavity infections, chronic suppurative otitis media, or postoperative infections as well as acute otitis externa were permitted only if the data for the acute otitis externa group were extractable.

Interventions

Additional Table 4 provides details of the treatment regimens used in the trials.

There were two multiple-intervention studies: Slack 1987 (three interventions) and van Balen 2003 (three interventions).

Ear cleaning

The definition and use of ear cleaning varied between studies. Ear cleaning was explicitly mentioned in 11 trials. Eight studies did not mention it. Of those utilising ear cleaning, nine performed it only on entry. The remaining two also utilised ear cleaning at subsequent visits. Studies that used ear cleaning rarely stated how this was

performed. Some studies were more specific and mentioned the use manual toileting or suction. Two studies were conducted in primary care; one study performed ear cleaning at the initial visit (van Balen 2003) and the other did not mention whether it was performed (Jones 1997).

Medicated wicks

The use of medicated wicks was variable. A number of studies permitted the use of medicated wicks at the start of the study if the ear canal was swollen. Patients were usually instructed to remove these themselves after a specific period of time and then administer the topical medication directly to the affected ear. Most wicks were used for 24 to 48 hours. All of the studies medicated their wicks with the appropriate trial intervention drug. Where wicks were used on an ad hoc basis, studies did not report their individual outcomes.

Topical treatments

Topical treatments consisted of drops, sprays or ointments.The following combinations were used in the trials included in this review:

- antiseptic;
- antibiotic;
- steroid;
- antibiotic/steroid;
- antiseptic/steroid;
- antiseptic/antibiotic/steroid;
- antibiotic/steroid/antifungal;
- antiseptic/astringent.

Most trials compared active treatments against each other. Two trials compared an active treatment against a placebo (Cannon 1967; Freedman 1978). One trial compared an oral antihistamine with topical steroid drops against an oral placebo with topical steroid drops (Emgard 1999).

Oral treatments

Two trials involved the use of systemic treatment:

- one trial involved an oral antibiotic;
- one trial involved an oral antihistamine.

Compliance

Compliance was assessed infrequently by trialists. Methods used include the evaluation of patient diaries and measurement of remaining bottled medication.

Outcomes

The 'Characteristics of included studies' table indicates which review outcomes were covered by each trial. Additional Table 5 describes the definitions used by the trials for each review outcome, and how and when outcomes were measured and reported.

Clinical response

Trialists often used a combination of clinical outcome measures when reporting results:

1. Cure rate - 12 trials

Over half of trials reported resolution of acute otitis externa as their primary outcome measure. Reporting results this way leads to binary outcomes which can be used in meta-analysis. The definition of complete resolution or cure varied between trials, some trials requiring the complete absence of symptoms and signs, whereas others permitted minor symptoms and signs to be present. The symptoms and signs evaluated by trialists were similar and included pain, itchiness, redness, swelling and discharge.

2. Clinical response - one trial

Where trials reported separate categories for completely successful, partially successful and unsuccessful, we have classed partially successful/satisfactory as failure along with any other cases of failure reported. Where trials did not report a completely cured category and just referred to responses as improvement versus no improvement, improvement has been classed as success.

3. Severity score - nine trials

Severity scoring systems varied from simple to more elaborate systems. Studies that used this method of outcome assessment handled the data in different ways. Some studies simply reported the mean change in severity scores for between groups, while others stipulated a priori that a certain reduction in symptom score would constitute a clinical improvement. The data from the latter group of studies is readily convertible into binary outcomes that can be used in meta-analysis.

4. Time to recovery - two trials

Neher 2004 reported time to complete disappearance of inflammation as determined by daily clinical examination. van Balen 2003 assessed time to recovery of symptoms according to daily patient diary entries.

5. Time to end of ear pain - one trial

Roland 2008 reported patient/caregiver assessments of time to end of pain.

6. Recurrence rate - one trial

van Balen 2003 assessed recurrence rate by telephone call at day 42.

7. Analgesic use - three trials

Analgesic consumption was documented by patients in their diaries.

Microbiological response

Only five trials evaluated a microbiological response to treatment, two utilising more than one method:

1. Microbial cure - two trials

In these trials microbiological swabs were taken at entry and at the end of treatment from each participant. Patients that had a positive culture at entry that subsequently became culture negative after treatment were classified as a microbial cure.

2. Eradication of pathogens - two trials

Microbiological swabs were taken on entry for each group as a whole and the number and frequency of each pathogen

documented (note: an ear with acute otitis externa may grow more than one pathogenic species). The process was repeated at the end of treatment. The reduction in the number of pathogenetic organisms for each group can therefore be calculated. This measure does not relate to individual patient outcomes and the authors of this review agreed a priori that these data would not be analysed as part of this review.

3. Clinical-microbiological response - three trials

These trials evaluated the microbiological evaluable population (i.e. those who had a positive culture at entry to the study). The number of participants that became culture negative after treatment was then determined. Those who were culture negative after treatment and were clinically cured after treatment constituted a clinical-microbiological success.

Adverse events

Adverse events were observed in nine trials. None were observed in five trials. Adverse events were not mentioned in five trials. Results of adverse events collected are reported in additional Table 6 (Safety).

Timing of outcome assessments

This varied between trials. All had baseline assessments on entry (day 1). Most conducted an assessment at an early stage (day three to five), one immediately at the end of treatment period (sometimes referred to as the end-of-treatment "EOT" visit) (day 7 to 10), and further assessments were usually conducted several days after treatment had finished (sometimes referred to as the test-of-cure "TOC" visit (day 14 to 21). Test-of-recurrence assessments were carried out from day 21 onwards.

Sources of support

Pharmaceutical companies supported six trials (Emgard 1999; Jones 1997; Mosges 2008; Roland 2004; Roland 2008; Schwartz 2006).

Trusts and charities supported two trials (Neher 2004; van Balen 2003).

Potential conflict of interest

Jones 1997 (two of the authors worked with the pharmaceutical company that manufactures ofloxacin - one of the drugs involved in the study).

Roland 2007 (one of the authors was an employee of the pharmaceutical company that manufactures ciprofloxacin/dexamethasone - one of the drugs involved in the study).

Roland 2008 (several authors are employees and stockholders of the pharmaceutical company that manufactures ciprofloxacin/hydrocortisone - one of the drugs involved in the study).

Risk of bias in included studies

Additional Table 1 provides details of the methodological quality of included studies.

Quality scores ranged from A to C. Only three trials were of high quality (Mosges 2008; Olivera 2004; van Balen 2003). The vast majority were of low quality (quality score = C) (13 trials). Three trials were of intermediate quality.

Sequence generation

Eight were 'adequate': Jones 1997; Masood 2008; Mosges 2007; Mosges 2008; Olivera 2004; Schwartz 2006; Tsikoudas 2002; van Balen 2003.

Eleven were 'unclear': described as randomised, but did not discuss how the sequence was generated, or how different diagnoses were accounted for during randomisation.

Allocation concealment

Eleven were 'adequate'.

Seven were 'unclear'.

In one study allocation concealment was not possible as the interventions were distinct from each other (Masood 2008).

Blinding

Eleven trials were double-blinded.

Eight were single-blinded.

Open/unblinded trials were excluded from this review.

Balance of baseline characteristics across group

Fifteen trials were balanced, although the degree varied between studies.

Two trials were unbalanced at baseline: Sabater 1996 and Slack 1987.

For the remaining two trials, the balance across groups on entry was not reported or was unclear.

Follow up (inclusion of randomised participants)

Nine trials were 'adequate' (> 90% included).

Five were 'borderline': Mosges 2007; Olivera 2004; Slack 1987; van Balen 2003 and Wadsten 1985.

Four were inadequate.

One trial was unclear: Roland 2007

Unit of analysis and handling of bilateral disease

Trials presented results either by participant or by ear. The handling of bilateral disease across trials was inconsistent. It is known that left and right ears are not independent. Consequently, trials involving patients with bilateral disease that reported results only at ear level were excluded to avoid any effect on interaural correlation on the analysis of the results. However, trials with bilateral disease were permitted if one of the ears was selected for study (trialists would consequently report results at participant level). Only a few trialists were explicit in their handling of bilateral disease (e.g. one ear was chosen through random selection and analysed; or the ear with the highest overall clinical score was designated the target ear and treated, the right ear being designated the target ear in the case of identical scores).

Additional Table 2 provides detailed information regarding the reporting of participants versus ears, and bilateral disease, for each trial.

Effects of interventions

Further detail is provided in the additional tables (Table 2 for details regarding bilateral disease in each trial, Table 4 for details of treatment regimens used, and Table 5 for the definitions and timings of outcomes assessed by trialists). Data relating to adverse events have been summarised in additional Table 6.

Clarification is being sought from authors where uncertainties exist in the data and where outcomes are not reported. These responses will be incorporated in subsequent updates of the review.

In this review the term "antimicrobial" refers to antiseptic or antibiotic.

Antimicrobial drops versus placebo drops

Two trials compared an antibiotic/steroid drops with placebo: Cannon 1967 and Freedman 1978.

Cannon 1967 evaluated methylprednisolone/neomycin and conducted follow up at day five and day 10. Ear cleaning was performed on the initial visit and again, if necessary, at day five and day 10 follow-up examinations. The drug vehicle comprised the placebo.

Freedman 1978 compared colistin/neomycin/hydrocortisone to a placebo starch solution. Both groups underwent ear cleaning at entry and on days three and seven. Results were reported using symptom severity scales. Binary outcomes that could be used in a meta-analysis were not reported.

Clinical cure

(Analysis 1.1)

The responses in Cannon 1967 were graded good, fair, none and worse. There was a significant effect in favour of the treatment group: OR 11 (95% CI 2.00 to 60.57). In percentage terms, a good response was obtained in 55% (11/20) of the active group compared with 10% (2/20) in the control group. The 10% cure rate in the control group is not readily explainable, although it seems most likely to be attributable to the drug vehicle. Other factors such as the process of ear cleaning or the underlying pathological inflammatory process burning itself out may have also contributed.

Freedman 1978 found significantly less oedema at day three ($P < 0.05$), and less itching, redness, scaling, weeping and pain at day seven ($P < 0.05$) in the active group. There were no significant differences in symptom severity scores at day 21.

Microbial cure

Not reported as an outcome by either trial. Freedman 1978 reported the effectiveness of each intervention at reducing overall pathogen counts in each group but data on how many individual patients in each arm were 'culture negative' at the end of the trial were not provided.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Quinolone versus non-quinolone antibiotic

One trial compared a quinolone with a non-quinolone with follow up at day eight (Sabater 1996). The trial compared ciprofloxacin with gentamicin.

Clinical cure

(Analysis 2.1)

There were no significant differences between groups.

Microbial cure

Not reported as an outcome.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antiseptic versus antibiotic

No trial compared an antiseptic with antibiotic. Trials comparing antibiotic/steroid with antiseptic/steroid were not included in this comparison category as steroids have their own therapeutic effect and vary in their potency. Their presence would confound the result and any meaningful interpretation.

Comparisons involving antibiotic/steroid

Antibiotic/steroid versus antiseptic

Three trials compared an antiseptic with an antibiotic/steroid (Neher 2004; Slack 1987; van Balen 2003). Follow up was unclear, unclear and 42 days respectively. Both Slack 1987 and van Balen 2003 were multiple-comparison trials.

The steroid components were as follows: hydrocortisone (Neher 2004; Slack 1987) and dexamethasone (van Balen 2003).

The antiseptics components were N-chlorotaurine (Neher 2004), boric acid (Slack 1987) and acetic acid (van Balen 2003).

The antibiotic component was the same in all trials: polymyxin B + neomycin.

Clinical cure

(Analysis 3.1)

The figure shows the results at seven to nine days, 14 days and 21 days.

The pooled result for all three trials at seven to nine days indicated a non-significant difference between the two interventions. However, there appears to be moderate heterogeneity observed in the results ($I^2 = 46\%$). Of these three pooled studies both Slack 1987 and Neher 2004 had a lower methodological quality score (B) compared with van Balen 2003 (A). Given the low number of studies involved in the meta-analysis and the fact that there are no outlying studies in terms of methodological quality it is unlikely that quality is the cause of the observed heterogeneity. Further inspection of the individual studies reveals a difference in the steroid components between the trials. van Balen 2003 used dexamethasone. The other trials used hydrocortisone. The glucocorticoid potency of hydrocortisone is low, whereas dexamethasone is high. In light of this it was decided to

combine only studies using the same steroid group and reassess homogeneity. Pooling Neher 2004 and Slack 1987 reduces I^2 to 0%. The pooled result at seven to nine days for these studies indicates no significant difference between the two groups: OR 3.46 (95% CI 0.65 to 18.53). The individual result for van Balen 2003 at seven days also indicates no significant difference between the two groups: OR 0.56 (95% CI 0.28 to 1.14).

Slack 1987 and van Balen 2003 reported at two weeks. Again, the steroid components were different and so the results of these studies were not combined. Taken in isolation only the study by van Balen 2003 shows a significant effect in favour of antibiotic/steroid: OR 0.29 (95% CI 0.13 to 0.62). Slack 1987 did not show any significant difference between groups: OR 4.38 (95% CI 0.15 to 125.29).

At three weeks all patients in both treatment arms were cured in the study conducted by Slack 1987. The results from van Balen 2003 at three weeks show a significant effect in favour of the antibiotic/steroid: OR 0.25 (95% CI 0.11 to 0.58).

Recurrence rate

(Analysis 3.2)

The figure shows the result of recurrence for between three and six weeks (van Balen 2003). There is a significant effect in favour of antibiotic/steroid: OR 3.12 (95% CI 1.37 to 7.09).

Time to healing

(Analysis 3.3; Table 2)

Two trials reported time to healing (Neher 2004; van Balen 2003). The result from Neher 2004 indicates that the time to healing was significantly better in the antiseptic group compared to the antibiotic/steroid group: 5.6 days versus 7.4 days respectively (mean difference: -1.80; 95% CI -2.69 to -0.91). This contrasts with the findings of van Balen 2003 in which the antibiotic/steroid group was significantly quicker to heal: 6.0 days (95% CI 5.1 to 6.9) versus 8.0 days (95% CI 7.0 to 9.0). The antibiotic components were the same. Neher 2004 used N-chlorotaurine (endogenous antiseptic) and hydrocortisone (low-potency steroid). van Balen 2003 used acetic acid (antiseptic) and dexamethasone (high-potency steroid). It is not possible to determine whether these conflicting findings are a result of differences in antiseptic potency and/or differences in steroid potency.

Microbial cure

Not reported as an outcome by any of these trials.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antibiotic/steroid versus antiseptic/steroid

One trial fell into this category (van Balen 2003). This was a three-arm trial. The relevant pair-wise comparison was selected for this section. Follow-up assessments were performed at day seven, 14 and 21.

The study compared a non-quinolone antibiotic/steroid with an antiseptic/steroid drop (polymyxin B + neomycin + dexamethasone versus acetic acid + triamcinolone).

Dexamethasone is a high-potency steroid. Triamcinolone is a medium-potency steroid.

Clinical cure

(Analysis 4.1)

No significant differences were found between treatment groups at week one, two or three.

Recurrence rate

(Analysis 4.2)

The figure shows the recurrence rate between three and six weeks. No significant difference was found between the two treatment groups.

Time to healing

(Table 7)

The median duration to recovery was six days (95% CI 5.1 to 6.9) in the antibiotic/steroid group compared to seven days (95% CI 5.8 to 8.3) in the antiseptic/steroid group. This result is not significant as the confidence intervals for each group overlap.

Microbial cure

Not reported as an outcome.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antibiotic/steroid versus antibiotic/steroid/antifungal

One trial compared an antibiotic/steroid drop with an antibiotic/steroid/antifungal drop (Slack 1987). This is a three-arm trial with follow up at one, two and three weeks.

Components: polymyxin B + neomycin + hydrocortisone versus polymyxin + flucinolone + econazole.

Steroid potency: hydrocortisone (low-potency steroid); flucinolone (low-medium potency steroid).

Clinical cure

(Analysis 5.1)

No significant differences were found between treatment groups at week one, two or three.

Microbial cure

Not reported as an outcome.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antibiotic/steroid versus antibiotic/steroid

Comparisons within this category were not pooled unless the interventions in each arm were identical (no trial satisfied this criteria).

Three trials compared an antibiotic/steroid with another antibiotic/steroid: Roland 2004, Roland 2007 and Wadsten 1985.

Follow up varied from day three to day 18.

Both Roland 2004 and Roland 2007 compared ciprofloxacin + dexamethasone with neomycin + polymyxin B + hydrocortisone.

Wadsten 1985 compared framycetin + gramicidin + dexamethasone against oxytetracycline + polymyxin B + hydrocortisone.

All were single-blind trials.

Roland 2004 was supported by a grant from Alcon Research Ltd who manufacture Ciprodex®.

Roland 2007 specifically evaluated the efficacy of two antibiotic/steroids in reducing otitis externa pain. They did not report clinical cures. One of the authors worked for Alcon Research Ltd.

Clinical cure

(Analysis 6.1)

Roland 2004 performed early assessments at day three and day eight. No significant differences were observed between groups at either of these time periods. However, at day 18 there was a significant effect in favour of ciprofloxacin/dexamethasone compared to neomycin/polymyxin B/hydrocortisone (OR 2.00; 95% CI 1.03 to 3.88).

Wadsten 1985 evaluated outcomes at two weeks. No significant differences were found between these non-quinolone antibiotic/steroid groups at this time.

Microbial cure

(Analysis 6.2)

One trial provided data on microbial cure (Roland 2004). The result at day 10 to 20 showed a significant effect in favour of quinolone/steroid compared to a non-quinolone/steroid: OR 2.94 (95% CI 1.33 to 6.50).

Relief of pain

Roland 2007 did not report binary outcomes. Patient reported results showed a higher percentage of ciprofloxacin/dexamethasone (quinolone/steroid) treated patients had relief of severe pain over time (P = 0.0013) and relief of significant pain (moderate and severe) over time (P = 0.0456). This group also had significantly less inflammation (P = 0.0043) and oedema (P = 0.0148) than neomycin/polymyxin B/hydrocortisone treated patients on day three. However, there was no difference between treatment groups in terms of percentage of patients who used no analgesics, non-narcotic analgesics or narcotic analgesics (P > 0.05).

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antimicrobial with steroid versus antimicrobial alone

Antibiotic/steroid versus antibiotic

Three trials compared an antibiotic/steroid drop with an antibiotic drop. Follow up varied: day 10+/-2 (Jones 1997), days 14 to 19 (Mosges 2008) and day 20 (Schwartz 2006). Mosges 2008 reported both binary and non-binary outcomes.

The steroid components were as follows: hydrocortisone (low-potency steroid) (Jones 1997; Schwartz 2006); dexamethasone (high-potency steroid) (Mosges 2008).

The antibiotic components were:

Jones 1997: neomycin + polymyxin B + hydrocortisone versus ofloxacin.

Mosges 2008: neomycin + polymyxin B + dexamethasone versus polymyxin B + neomycin.

Schwartz 2006: neomycin + polymyxin B + hydrocortisone versus ofloxacin.

The interventions compared by Jones 1997 and Schwartz 2006 are the same.

Mosges 2008 reported binary outcomes at day 10+/-2. As it used a high-potency steroid the results were not pooled with the other two trials which used a low-potency steroid.

Clinical cure

(Analysis 7.1; Table 8; Table 9)

The result at day seven to nine (Schwartz 2006) shows a significant result in favour of quinolone antibiotic: OR 1.96 (95% CI 1.07 to 3.61).

The pooled result at days 14 to 20 for Jones 1997 and Schwartz 2006 is homogenous (I^2 = 0%). No significant differences were found between non-quinolone antibiotic/steroid and quinolone antibiotics at these times: OR 1.03 (95% CI 0.61 to 1.75). However, the individual result for Mosges 2008 shows a significant benefit in favour of the non-quinolone antibiotic/steroid group compared with the non-quinolone at this time point: OR 0.61 (95% CI 0.39 to 0.94).

Mosges 2008 also reported non-binary outcomes.There were no significant differences in individual symptom scores between groups across visits 1 to 2 (day 1 to 4+/-1), and visits 1 to 3 (day 1 to 10+/-2), except for reduced swelling in the antibiotic/steroid group between visits 1 to 2 (P = 0.03). Similarly, there were no significant differences in VAS (visual analogue scale) scores or paracetamol consumption rates between the two groups across these time frames. Patient global assessment of efficacy at visit 3 revealed that patients favoured the antibiotic/steroid over the antibiotic alone in both 2 and 4 category ratings of efficacy (P = 0.01 and P = 0.05 respectively).

Microbial cure

No trials reported this outcome.

Overall clinical-microbiological response

(Analysis 7.2)

This refers to the number of patients who were clinically cured and were culture negative at the end of therapy for the assumed pathogenic organism. It therefore only evaluates the microbiologically available population. No significant difference

was found between antibiotic/steroid and antibiotic at day seven to nine (Schwartz 2006) or the pooled result at day 14 to 20 (Jones 1997; Schwartz 2006) (I^2 = 25%).

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antiseptic/steroid versus antiseptic

Only one trial compared an antiseptic/steroid with an antiseptic (van Balen 2003). This was a three-arm trial. Duration of follow up was 42 days and treatment was up to 21 days. The antiseptic was acetic acid in both arms. The steroid comprised triamcinolone (medium-potency steroid).

Clinical cure

(Analysis 8.1)

The figure shows the results at weeks one, two and three. The results are significantly in favour of the acetic acid with triamcinolone compared with acetic acid alone, the effect becoming increasingly significant with time: OR 2.19 (95% CI 1.05 to 4.57), 2.32 (95% CI 1.08 to 4.97) and 4.82 (95% CI 1.90 to 12.25) respectively. For the acetic acid only group the percentage cure rates at the respective time points were 29.2% (19/65), 56.9% (37/65) and 61.5% (40/65).

Recurrence rate

(Analysis 8.2)

No significant difference was found between groups at three to six weeks: OR 0.44 (95% CI 0.19 to 1.01).

Time to healing

(Table 7)

The median duration to recovery was seven days (95% CI 5.8 to 8.3) in the antiseptic/steroid group compared to eight days (95% CI 7.0 to 9.0) in the antiseptic group. This is not significant as the confidence intervals overlap.

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Comparisons involving a steroid-only group

Antibiotic/steroid versus steroid alone

One trial compared an antibiotic/steroid with a steroid-only drop. Follow-up assessment was carried out at day 11 (Tsikoudas 2002).

The steroid component was betamethasone (high-potency steroid) and the antibiotic component was neomycin.

Tsikoudas 2002 did not report results by binary outcomes. Instead, assessment scores were compared across groups at day 11, using P values.

Clinical cure

(Table 10)

No statistically significant difference was demonstrated between the antibiotic/steroid group and the steroid group, for either patient or observer assessments at day 11.

Microbial cure

No trials reported this outcome.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Oral antihistamine + steroid drop versus oral placebo + steroid drop

One trial compared an oral antihistamine plus topical steroid against oral placebo and the topical steroid (Emgard 1999). Follow up was at three weeks. The steroid component was exactly the same in both arms (betamethasone: a high-potency steroid). The oral antihistamine was loratadine.

Sixty percent (18/30) of patients in the trial showed clinical findings of infection and underwent sampling for ear culture. Of 18 cultures 14 showed positive findings. No antibiotics were allowed as part of the protocol, even if culture was positive. It was also reported that no difference in the improvement of the ear canal status was observed during treatment of infected cases compared with non-infected cases.

Clinical cure

(Analysis 9.1)

No significant difference was found between the two groups at three weeks (OR 3.21; 95% CI 0.12 to 85.20), suggesting that the addition of an oral antihistamine to topical therapy does not influence outcome. In the oral antihistamine and topical steroid group 100% were cured. In the steroid drop alone (control) group 94% were cured.

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Comparisons involving medicated wicks

Antibiotic/steroid versus antibiotic

Mosges 2007 compared an antibiotic ointment with an antibiotic/steroid. (Table 11). The antibiotic was the same in both cases (polymyxin B and bacitracin). The steroid was hydrocortisone (low-potency steroid).

A medicated gauze strip was inserted on day 1 and removed by the patient after 24 hours. Ointment was then applied twice daily. Another medicated gauze strip was inserted on day three to five and again removed 24 hours later by the patient. Ointment was then applied twice daily until day 10.

The authors did not report results by binary outcomes. There were no significant differences between groups in terms of aggregate clinical severity scores between entry and day three to five (P = 0.3514), or between entry and day 9 to 11 (P = 0.1440).

A significant difference in subscores was noted for resolution of "severe" redness (P = 0.045) and secretion (P = 0.024), from entry to day nine to 11 in the antibiotic/steroid group compared with antibiotic alone. Most trial participants did not require paracetamol for pain relief, but of those that did, significantly fewer paracetamol tablets were consumed by the antibiotic/steroid group (P = 0.0455). However, this result was not reflected in the reduction of visual analogue scores for pain from entry to day three to five, and from entry to day nine to 11, which were similar across the groups (P = 0.8737 and P = 0.7255 respectively).

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antifungal/antibiotic/steroid versus antiseptic/astringent

One trial compared antifungal/antibiotic/steroid ointment on wick with an antiseptic/astringent solution on a wick for 48 hours in the initial treatment of severe acute otitis externa (Masood 2008). Patients were evaluated at 48 hours. Results were not reported by binary outcomes. The components were as follows: nystatin + gramicidin + neomycin + triamcinolone versus glycerine + ichthammol.

Clinical response

(Table 12)

No significant difference in mean sign score improvement was noted between entry and day three between the two interventions (P = 0.979). However, a significant improvement in mean pain score was noted in the antifungal/antibiotic/steroid group (P < 0.001).

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Comparisons involving oral antibiotics

Oral antibiotic + antibiotic/steroid drop versus antibiotic/steroid drop

One trial compared an oral antibiotic plus topical non-quinolone antibiotic/steroid drop against a topical quinolone antibiotic/steroid drop alone (oral amoxicillin with neomycin + polymyxin B + hydrocortisone versus ciprofloxacin + hydrocortisone) (Roland 2008). Both binary and non-binary outcomes were reported. The steroid component in both groups was hydrocortisone (low-potency steroid).

Clinical-microbial response

(Table 13)

Patients were deemed to have 'responded' to therapy if physician assessment at end-of-therapy visit was "improved" or "cured", and if microbiological eradication could be presumed or confirmed at the end-of-therapy or test-of-cure visit. No significant differences were found between the treatment groups (P = 0.5109; 95% CI -4.98 to 13.89).

Microbial cure/eradication

(Table 13)

No significant differences were found between the two groups in terms of microbial eradication (P = 0.4086; 95% CI -3.60 to 11.84).

Time to end of ear pain

(Table 13)

No significant difference occurred in mean time to end of ear pain between groups (P = 0.9644).

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Comparisons involving sprays

Antiseptic/antibiotic/steroid versus antiseptic

One trial compared an antiseptic/antibiotic/steroid spray with an antiseptic spray (Johnston 2006). Follow up was at two and four weeks. The antiseptic was the same in both groups (glacial acetic acid). The other components were dexamethasone (high-potency steroid) and neomycin (antibiotic).

Clinical cure

(Analysis 10.1)

The figure shows results at weeks two and four. At both stages there is a significant difference in favour of antiseptic/antibiotic/steroid compared to antiseptic only spray (acetic acid): OR 0.24 (95% CI 0.07 to 0.79) and 0.10 (95% CI 0.02 to 0.41) at two and four weeks respectively.

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Other comparisons

Glycerine versus aqueous vehicle

Olivera 2004 investigated the use of a glycerine vehicle compared with an aqueous solution for a quinolone drop, with follow up at week 1.

Clinical cure

(Analysis 11.1)

All patients in both groups were cured.

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

Antiseptic versus antibiotic/steroid/antifungal

One trial compared an antiseptic drop (boric acid) with an antibiotic/steroid/antifungal drop (polymyxin + flucinolone + econazole) (Slack 1987).

Clinical cure

(Analysis 12.1)

No significant differences were found between treatment groups at week one, two or three.

Microbial cure

Not reported as an outcome by this trial.

Adverse events

Data relating to adverse events have been summarised in additional Table 6.

DISCUSSION

Summary of main results

For uncomplicated acute otitis externa the use of a topical antimicrobial (antibiotic or antiseptic), with or without steroid, is highly effective. Trials report a 55% to 100% cure rate. In comparison, instillation of drug vehicle (placebo drops) accompanied by ear cleaning only achieves a cure rate of 10%.

Cleaning of the ear canal

No trial specifically endeavoured to evaluate the efficacy of cleaning of the ear canal. It is performed at entry to most trials in order to secure the diagnosis of acute otitis externa and permit evaluation of the response to treatment. Ear cleaning is performed frequently in secondary care to help treat refractory cases of acute otitis externa associated with very swollen ear canals or copious amounts of debris and discharge. In contrast, it is rarely performed in primary care where the vast majority of cases of acute otitis externa are successfully treated. It would be useful to be able to quantify the effect of this intervention through a future trial.

Quinolone versus non-quinolone

Evidence is limited to one trial of moderate quality (Sabater 1996). Similar clinical outcomes were found in the quinolone and non-quinolone groups. The outcomes observed in trials comparing quinolone/steroid against non-quinolone/steroid were also equivalent (Roland 2004 and Wadsten 1985). Roland 2004 did show a significant difference in favour of quinolone/steroid at day 18 (OR 2.00; 95% CI 1.03 to 3.88). However, the lower limit of this confidence interval approaches 1.0 suggesting that negligible differences cannot be excluded. With regard to microbial cures in this trial, a significant difference in favour of quinolone/steroid was demonstrated at day 18: OR 2.94 (95% CI 1.33 to 6.50); this statistically significant result is also questionable as there was a significant difference in the distribution of gram positive and gram negative strains between treatment groups at baseline (P = 0.041). Roland 2007 reported that their quinolone/high-potency steroid group had significantly more relief of severe and significant pain over time (P = 0.0013 and P = 0.0456) and less inflammation (P = 0.0043) and oedema (P = 0.0148) compared to the non-quinolone/low-potency steroid group. It is likely that the observed difference in anti-inflammatory effects and pain relief are attributable to the difference in steroid potency between the two groups rather than the difference in antibiotic class. They did not report binary outcomes and so it is not possible to determine the magnitude or precision of their observed effect. The fact that no differences were found in analgesic use between the two groups (P > 0.05) suggests that their statistically significant results may not be clinically meaningful.

Antiseptic versus antibiotic

No evidence is available for assessment.

Antibiotic/steroid versus antiseptic

Evidence is available from three trials (Neher 2004; Slack 1987; van Balen 2003). No difference was found between antibiotic/steroid and antiseptic in terms of clinical efficacy, with one exception: acetic acid drops did not perform well against non-quinolone antibiotic/high-potency steroid drops at two time points (they were comparable at seven days, but not at two and three weeks (OR 0.29 (95% CI 0.13 to 0.62), OR 0.25 (95% CI 0.11 to 0.58)) (van Balen 2003). Recurrence at three to six weeks was also in favour of antibiotic/steroid: OR 3.12 (95% CI 1.37 to 7.09). In addition, the antibiotic/steroid group was significantly quicker to heal: 6.0 days (95% CI 5.1 to 6.9) versus 8.0 days (95% CI 7.0 to 9.0). In contrast, Neher 2004 found that the antiseptic group healed more quickly: mean difference (MD) -1.80 days (95% CI -2.69 to -0.91). It is not possible to determine whether these conflicting findings are a result of differences in antiseptic potency, differences in steroid potency or a combination of the two.

It is interesting to evaluate the performance of the acetic acid alone group (van Balen 2003). The cure rate at one, two and three weeks was 19/65 (29.2%), 37/65 (56.9%) and 40/65 (61.5%) respectively. Treatment for acute otitis externa is generally prescribed for seven to 10 days. Based on the results this study the seven to 10-day cure rate for acetic acid is likely to be at the lower end of the 29% to 56% range. Also noteworthy is that between two and three weeks only three additional participants were cured. Recurrence at three to six weeks is unlikely to be a strong indicator of a treatment's long-term benefit as it may be influenced by a number of other factors, such as the patient resuming swimming activities.

Antibiotic/steroid versus antiseptic/steroid

Evidence is limited to one high quality trial (van Balen 2003). No significant differences were noted between the two interventions. The antiseptic/steroid was acetic acid with triamcinolone.

Antibiotic/steroid versus antibiotic

Evidence from three trials is available (Jones 1997; Mosges 2008; Schwartz 2006). Clinical and clinical-microbiological outcomes were similar in both groups. Findings of Schwartz 2006 at days seven to nine, and Mosges 2008 at days 14 to 19 were significant, but confidence interval limits approach 1.0 suggesting that negligible

differences cannot be excluded. The trial by Mosges 2008 was an ideal way of testing the effect of adding a steroid to an antibiotic as the antibiotic was the same in each group (unlike Jones 1997 and Schwartz 2006). Polymyxin B/neomycin was compared with dexamethasone/polymyxin B/neomycin. Primary outcome measures were reported in non-binary form. Reduced swelling was noted in the antibiotic/steroid group between day one and four (P = 0.03). Patient global assessment of efficacy at the final visit suggested patients significantly favoured the antibiotic/steroid over the antibiotic alone, although this is a subjective measure and warrants cautious interpretation. Overall it appears that adding a high-potency steroid to an non-quinolone antibiotic drop does not affect cure rate, but may reduce swelling, although it is not possible to determine the magnitude or precision of the results as only P values were reported.

Antiseptic/steroid versus antiseptic

Evidence is limited to one trial (van Balen 2003). Adding triamcinolone (medium-potency) steroid to acetic acid drops significantly improved cure rate at three weeks: OR 4.82 (95% CI 1.90 to 12.25). Although the results at one and two weeks and the recurrence rate at three to six weeks were statistically significant the limits of these confidence intervals approach 1.0 suggesting that negligible differences cannot be excluded (OR 2.19 (95% CI 1.05 to 4.57); 2.32 (95% CI 1.08 to 4.97); 0.44 (95% CI 0.19 to 1.01) respectively). From the authors' experience, treatment for acute otitis externa is usually given for seven to 10 days and in some cases for up to two weeks; at these time points the outcomes for both groups were not assuredly different and thus the findings at three weeks are unlikely to be clinically significant. Time to healing was similar for both groups.

Antibiotic/steroid versus steroid alone

Evidence is limited to one trial (Tsikoudas 2002). The clinical outcomes were similar in both groups (patient assessment P = 0.3 and observer assessment P = 0.164). P values were used and so it is not possible to determine the magnitude or precision of the effect. The trial was also of low quality. One must therefore interpret the result with caution.

Oral antihistamine + steroid drop versus steroid drop alone

Evidence is limited to one trial of moderate quality (Emgard 1999). Clinical outcomes were similar in both groups. This supports the findings by Tsikoudas 2002.

It has been suggested that using steroid drops alone is effective in treating acute otitis externa. Whilst most clinicians would be happy to prescribe them for cases of eczematous otitis externa, there is reluctance to use them in cases of acute otitis externa exhibiting mucopurulent discharge. In addition there is concern that the sole use of a steroid may render patients susceptible to developing secondary fungal otitis externa. The relevant studies in this review did not report any such problem. However, a personal communication with the author of one trial (Hilmi 2001), which was subsequently abandoned because of this very problem, would suggest that there may be a degree of publication bias. Further investigation is warranted into the efficacy of steroid only drops with a well-designed trial.

Antibiotic/steroid versus antibiotic (ointment on wicks followed by ointment application only)

Evidence is limited to one trial (Mosges 2007). The trial design was an ideal way of testing the effect of adding a low-potency steroid (hydrocortisone) to an antibiotic as the antibiotic was the same in each arm. Clinical outcomes were similar. However, subgroup analysis revealed resolution of "severe" redness (P = 0.045) and secretion (P = 0.024), from entry to day nine to 11 in favour of the antibiotic/steroid group. In addition significantly less paracetamol was consumed in the antibiotic/steroid group (P = 0.0455), although pain score reductions across groups were comparable. P values were reported and so it is not possible to determine the magnitude or precision of these secondary endpoints.

Antifungal/antibiotic/steroid versus antiseptic/astringent (on medicated wicks)

Evidence is limited to one trial (Masood 2008). This trial specifically set out to evaluate pain relief provided by two commonly used methods in the early treatment of severe acute otitis externa. Sign scores were comparable at 48 hours. Pain scores were significantly less in the antiseptic/astringent group (P < 0.001). As P values were used it is not possible to determine the magnitude or precision of the result.

Oral antibiotic + antibiotic/steroid drop versus antibiotic/steroid drop

Evidence is limited to one trial (Roland 2008). Similar outcomes were found in both groups suggesting that oral antibiotics are not required in the treatment of simple acute otitis externa. The high cure rates observed in the topical-only trials in this review further supports this.

Antiseptic/antibiotic/steroid versus antiseptic (sprays)

Evidence is limited to one trial (Johnston 2006). The sprays were continued until cure. Acetic acid spray is clinically less effective compared to acetic acid/non-quinolone/high-potency steroid spray: OR 0.24 (95% CI 0.07 to 0.79) and 0.10 (95% CI 0.02 to 0.41) at two and four weeks. Furthermore, no additional patients in the acetic acid spray group were cured between the second and fourth week assessment points (12/32 (37.5%) and 12/32 (37.5%) at two and four weeks respectively). Acetic acid is a weak acid and this may be a reason for its lack of performance in spray and droplet form (see 'Antibiotic/steroid versus antiseptic' and 'Antiseptic/steroid versus antiseptic' comparisons above). However, since boric acid (also a weak acid) (Slack 1987) performs equally well in comparison to interventions such as antibiotic/steroid drops or antibiotic/steroid/antifungal drops there is likely to be some other explanation.

Time to recovery

Two trials investigated time to recovery (van Balen 2003 and Neher 2004). van Balen 2003 defined this as duration of symptoms according to daily patient diary entries. Neher 2004 assessed patients daily and defined the time to recovery as the time required for signs of inflammation to resolve. Neher 2004 applied the medication to wicks which were subsequently inserted into the ear canal and changed on a daily basis in clinic; as this is method is unlikely to be reproducible in everyday clinical practice we decided to concentrate on the results of van Balen 2003.

In the study conducted by van Balen 2003 patient diaries showed that the median duration to recovery of symptoms when using antibiotic/steroid drops was 6.0 days (95% confidence interval of 5.1 to 6.9 days). Investigator assessment performed at day seven showed a cure rate of only 42% (31/73). The cure rate rose to 82% (60/73) at the second visit at day 14. It increased by just 4% (3/73) during continued treatment from day 14 until day 21. Although the overall cure rate for the group improved as treatment continued it is apparent that no substantial benefit was gained when treatment was continued beyond 14 days.

In clinical practice a seven to 10-day course of topical medication is usually prescribed. Patients with more severe infections may require 10 to 14 days of treatment. It is commonly recommended that drops be given for three days beyond the cessation of symptoms (Sander 2001). This advice attempts to treat residual inflammation within the ear canal (resolution of clinical signs lags behind that of symptoms). It is unclear whether this practice confers any benefit.

The study by van Balen 2003 illustrates the fact that a standard seven to 10-day course of topical medication will overtreat some patients and undertreat others. In reality it is likely that patients whose symptoms subside during the standard treatment period discontinue their therapy, and those with symptoms persisting beyond the prescribed period self-medicate for a while, until they are cured or deem it necessary to see a doctor because they are not. Therefore from a practical standpoint, it may be more useful when prescribing ear drops to instruct the patient to use them for at least a week. If they still have symptoms beyond the first week they should continue the drops until their symptoms resolve (and possibly for a few days after) for a maximum of a further seven days. It would seem reasonable to say that patients with symptoms beyond two weeks should be considered treatment failures and alternative management initiated.

Methodological quality

Only three studies were of high quality. Eleven trials were double-blind and eight were single-blind. Only 11 studies performed adequate allocation concealment. It has been shown that trials which are not double-blind yield larger estimate of effects, with odds ratios being exaggerated by 17%. Similarly, trials in which concealment is either unclear or inadequate will exaggerate the estimate of effect by 30% and 41% respectively (Shulz 1995). Consequently, our pooled results will have an inherent tendency to overestimate efficacy.

Setting

All but two of the trials included in this review were conducted in specialist clinics. This does not reflect the pattern of care provision observed in clinical practice; in many countries cases of acute otitis externa are seen and treated successfully in primary care without the need for ear cleaning. Indeed, a recent study noted that only 3% of patients with acute otitis externa attending general practice in the UK needed referral to an ENT specialist (Rowlands 2001). The disproportionate number of secondary care trials in this review will affect the generalisability of the results to primary care.

Follow-up period

The follow-up period was variable. Most studies conducted an assessment at the end of treatment, followed by a further assessment, usually a week later, sometimes referred to as a 'test-of-cure visit'. Acute otitis externa is a condition where patients can develop relapse within a few weeks of the initial episode. One investigator performed an assessment of recurrence by telephoning patients at day 42 (van Balen 2003). As this outcome measure could be influenced by several other factors (e.g. the patient returning to swimming) it is unlikely to provide a strong or direct indicator of a treatment's long-term benefit.

Adverse events

Most trials did not report any adverse events. Those that did occur were usually mild and did not necessitate discontinuation of treatment. No trial reported any significant difference in treatment-related adverse events between intervention groups. No study reported contact dermatitis associated with neomycin or aminoglycosides.

Microbiology

As with any randomised controlled trial, both groups should be reasonably matched at baseline to ensure that any observed therapeutic difference can be attributed entirely to the intervention(s) under review. Most studies ensured that parameters such as demographics and severity of disease were matched at entry. However, only a few studies compared bacteriological populations at baseline.

Six trials used a microbial outcome measure. One method employed was to determine the effectiveness of interventions' ability to reduce the pathogen count between entry and the end of treatment for each group as a whole. However, as this data does not relate to individual patient outcomes its usefulness is very limited.

Evaluation of microbial cures was the other method used. Microbial cures are those participants who had a positive baseline culture and returned at the end of treatment and were culture negative. However, there are potential flaws with this outcome measure that may limit the interpretation of such data. Firstly, there is the complex issue of whether organisms recovered in patients with acute otitis externa are actually responsible for the inflammation in all cases, or whether some are commensals which play no part in its pathogenesis.

Secondly, we know that changes in this surrogate endpoint do not rapidly and accurately reflect the clinical response to treatment; the incidence of bacteriologic cure tends to exceed the clinical response (Rosenfeld 2006).

In addition, the persistence of bacteria in the ear canal following treatment does not necessarily imply persistent acute otitis externa symptoms or clinical failure.

Finally, both microbial and combined clinical-microbiological results are only generalisable to the microbiologically evaluable population. If applied to the clinically evaluable population the effect size is further reduced.

Despite all of this, it remains a useful measure to refer to when a clinically significant outcome is observed as one would expect the microbiological cure data to be concordant.

Intention-to-treat versus per-protocol analysis

Intention-to-treat is a strategy for the analysis of randomised controlled trials that compares patients in the groups to which they were originally randomly assigned regardless of whether they completed treatment, deviated from protocol, or withdrew from the study (Hollis 1999). Intention-to-treat analyses are generally preferred as they are unbiased and also because they address a more pragmatic and clinically relevant question (Handbook 2008). We chose to use per-protocol denominators in the meta-analyses, as only three trials (Jones 1997; Roland 2004; van Balen 2003) explicitly stated their intention-to-treat denominators. Use of intention-to-treat denominators, if they were available, would have reduced the pooled effect size in all related meta-analyses.

Generalisability

Are the results of this review generalisable to a general practitioner treating a patient with acute otitis externa in primary care? As with any trial or systematic review, the results are only applicable to the specific population studied, the intervention(s) performed and the setting in which it was conducted. The generalisability of this review is restricted by a number of factors:

Exclusion criteria varied considerably between trials from none whatsoever to exhaustive lists of conditions. Results from studies with tight exclusion criteria will only truly be applicable to the restricted population studied.

Most of the studies were conducted in secondary care. It is conceivable that patients recruited from specialist clinics are likely to suffer from a more severe form of acute otitis externa compared to those attending their general practitioner. The extent to which the results of this review are generalisable to primary care is therefore somewhat diminished.

Cleaning of the ear canal was explicitly mentioned in 11 of the 19 trials. This practice is unlikely to be available in primary care where the vast majority of cases of acute otitis externa present. In this respect, the results of these 11 trials will not be truly applicable to those patients attending their general practitioner with the condition. However, one must take a reasoned view and temper this critique with the fact that trialists clean the ear canal at trial entry for pragmatic reasons. It allows an intact tympanic membrane to be visualised (and therefore a diagnosis of chronic suppurative otitis media to be excluded), permits assessment of the ear canal before treatment commences, and allows the response to treatment to be assessed. Indeed, one or more of these factors may have been the underlying reason why one of the primary care trialists chose to perform ear cleaning at the initial visit (van Balen 2003) (the other trial conducted in primary care did not mention whether ear cleaning was performed). If we assume that removal of debris and discharge from the ear can make a topical drop more effective at treating acute otitis externa, then the results of this systematic review are likely to represent an overestimate of effect size.

As mentioned earlier, any microbial results are only generalisable to that smaller subset of patients that comprise the microbiologically evaluable population.

The microbiology of otitis externa varies across the world. Candida, aspergilli and other species of fungi are found in about 80% of tropical cases of otitis externa, but the proportion in the UK is much smaller (10% to 20%) (Barton 1979). The vast majority of studies in this review were conducted in temperate climates and as such the results may not be applicable to other geographical locations.

Compliance was monitored in only a few studies. Although these data provide us with an indication of whether the medication was used, they do not inform us whether the drops were administered correctly. It is likely that drops were administered suboptimally and insufficiently in most trials, but this is likely to be a true reflection of how this occurs in real life, so is unlikely to affect the generalisability of the results.

Pooling of data

Trialists measured their outcomes on different days. The data from studies included in this review were only combined in meta-analysis if their interventions matched in terms of their constituent drug category and the data were taken from the same time interval. Statistical pooling of data was possible on three occasions, across two comparisons. Many studies reported symptom severity scores. Unfortunately these could not be combined statistically because of heterogeneity or incomplete reporting (e.g. no standard deviation).

Heterogeneity

Heterogeneity was found in our first meta-analysis. Initially it was not readily explainable and did not appear to be related to quality, study population or outcome measures. However, it became apparent that it was related to steroid potency. Consequently, only pooling of interventions containing similar steroid potencies was permitted.

Other systematic reviews

During the writing of this review a systematic review of topical antimicrobial therapy for acute otitis externa was published (Rosenfeld 2006).

Twenty trials met their inclusion criteria with 18 having data suitable for pooling. They investigated the following comparisons: antimicrobial versus placebo; antiseptic versus antimicrobial; quinolone antibiotic versus non-quinolone antibiotic; steroid-antimicrobial versus antimicrobial; and antimicrobial-steroid versus steroid. All clinical comparisons except two were non-significant: antimicrobial versus placebo, and antimicrobial-steroid versus steroid. The authors concluded that topical antimicrobial therapy was highly effective at treating acute otitis externa. They also reported that steroid-only drops increased cure rates by 20% compared with steroid plus antibiotic (95% CI 3% to 38%). Minor differences in comparative efficacy between topical antimicrobials were noted but it was felt that these were unlikely to be of any clinical significance. Quinolone drops increased bacteriologic cure rates by 8% compared with non-quinolone antibiotics (95% CI 1% to 16%), but had statistically equivalent rates of clinical cure and adverse events.

The main differences between the systematic review and meta-analysis by Rosenfeld 2006 and our review are as follows:

Identification of studies

We identified three additional studies published during their search period (1966 to July 2005) and included them in our review (Emgard 1999; Olivera 2004; Wadsten 1985). Six trials published subsequent

to their review have also been included (Johnston 2006; Masood 2008; Mosges 2007; Mosges 2008; Roland 2007; Roland 2008).

Characteristics of included studies

Open trials were included in their review; we excluded them (Arnes 1993; Emgard 2005; Goldenberg 2002; Lambert 1981; Pistorius 1999; Psifidis 2005).

Studies with bilateral disease in which both ears were analysed were allowed in their review (Kime 1978; Ordonez 1978); we excluded them.

Their review permitted trials that included other diagnoses, where randomisation was not stratified by diagnosis (Cannon 1970; Clayton 1990); we excluded them.

We excluded Ruth 1990. This study permitted aluminium acetate wicks for any case with a swollen ear canal as a prelude to the intervention assigned by randomisation. No detail was provided on the number of participants that required these wicks, the numbers in each group or their individual outcomes. We decided not to include this trial as this measure is likely to have confounded the overall result.

Analysis

There are subtle but important differences in way in which the results were analysed. The "antiseptic versus antibiotic" comparison category in their review included treatments containing steroids. We chose to analyse trials containing steroid components separately as the steroid component will have had its own therapeutic effect and is likely to have confounded the result. This same applies to their "quinolone versus non-quinolone" comparison, which also included treatments containing steroids.

Overall these differences resulted in their review having 13 meta-analyses compared to only three in our review.

Placebos

Most trials compared active treatments. Three trials involved the use of a placebo. Of these, two investigated the efficacy of antibiotic/steroid drops; one trial used the drug's vehicle as placebo and the other a starch solution.

Although placebo controlled trials are considered by many to provide the best assessment of efficacy their use can be problematic. Firstly, the use of a placebo raises ethical issues; it leaves individuals who receive it, but are in need of actual medication for their condition, untreated. Furthermore, patients are less likely to participate in trials in which they may be randomised to an inactive treatment.

Secondly, it is not always easy to find a placebo that is inactive. Water or water-containing solutions (e.g. starch solution) may act as nocebos (cause a negative placebo effect) due to maceration of the ear canal. Some trialists have used the drug's vehicle as placebo. In Cannon 1967, the antibiotic/steroid group (with drug vehicle) achieved a 55% good response rate compared with 10% for the drug vehicle alone, the inference being that the true efficacy of the antibiotic/steroid by itself was 45%. The composition of drug vehicles can vary and consequently so can their therapeutic effect. Trials using drug vehicle placebos can therefore help us precisely quantify the effectiveness of the active ingredient.

Carrying agents

In this review interventions were classified according to drug category. This was determined by the main active ingredient(s). The following groups were used: antiseptic (we included acidifying agents in this group), astringent, antibiotic, steroid, antifungal or combinations of the aforementioned. Although it is convenient to compartmentalise these medications to allow easier comparison, the whole premise may be over simplistic. It is important to realise that many treatments rely on a drug vehicle (carrying agent) and/or preservative in order for them to remain stable and be administrable in droplet or spray form. These chemicals (which include thonzonium bromide, benzalkonium chloride and propylene glycol) can have a therapeutic effect of their own. Indeed, the 10% cure rate observed in the drug vehicle group (placebo) in the trial performed by Cannon 1967 is a case in point. Factors such as the pH of the solution may also have an effect.

One consequence of this naming strategy is that medications falling into a specific drug category (because they share a common active ingredient) could have different vehicles and preservatives associated with them. Consequently, whenever a statement is made regarding the efficacy a specific drug category it will not be a true reflection of the effectiveness of the main active ingredient.

In addition, for any given treatment it will be difficult to ascertain whether an observed therapeutic effect is wholly or only partly attributable to the 'active' ingredient. This raises the question of whether cures seen in trials using steroid-only drops are a result of the steroid's action on the underlying pathogenesis of acute otitis externa or due to the chemical preservatives, such as benzalkonium chloride, accompanying them. A trial comparing a steroid-only drop with its drug vehicle acting as a placebo would help clarify this.

AUTHORS' CONCLUSIONS

Implications for practice

High quality level 1 evidence regarding interventions for acute otitis externa is sparse. The comparison categories studied in this review mostly contain single trials only. Only three meta-analyses were possible. Results are largely based on odds ratios calculated from single trials, most of which have very broad 95% confidence intervals because of small to modest sample sizes. A number of significant results have 95% confidence intervals whose limits approach 1.0, suggesting that negligible differences cannot be excluded. A number of recent trials report results using P values that do not allow the magnitude or precision of the results to be evaluated, and as a result any findings merit cautious interpretation. The findings of this systematic review may not be wholly generalisable to primary care for a variety of reasons; only two of the 19 trials included in the review were conducted in a primary care population setting, and 11 of the 19 trials had ear cleaning as part of the treatment. Having said all of this, a few salient points can be made from the evidence available:

Topical treatments alone are effective for uncomplicated acute otitis externa. Additional oral antibiotics are not required.

In most cases the choice of topical intervention does not appear to influence the therapeutic outcome significantly. Any observable

differences in efficacy were minor and not consistently present at every assessment point.

Evidence from one trial (Sabater 1996) of low quality found no difference in clinical efficacy between quinolone and non-quinolone drops. Quinolones are more expensive than non-quinolones. This finding may influence their use in cost-driven and resource-poor settings.

If treatment needs to be extended beyond one week acetic acid alone appears to perform less well when compared against other topical treatments. One high quality trial (van Balen 2003) compared acetic acid with antibiotic/steroid drops; although the cure rate was comparable at day seven to nine it was poorer in the acetic acid group at weeks two and three. A separate trial, of low quality, showed that acetic acid spray had a poorer cure rate than acetic acid/antibiotic/steroid spray at two and four weeks (Slack 1987). Acetic acid is available in many countries as a non-prescription remedy at low-cost, in both drop and spray form. The manufacturer recommends using it for a maximum of seven days. The results from van Balen 2003 support their use for this duration. However, their study also showed that symptoms were more prolonged in the acetic acid group (eight days versus six days in the antibiotic/steroid group); this may influence the decision to use acetic acid in primary care.

There is some evidence which indicates that patients treated with topical antibiotic containing steroid benefit from reduced swelling (Mosges 2008), severe redness, secretion and analgesic consumption (Mosges 2007) compared to their non-steroid counterpart. There is a suggestion that high-potency steroids may be more effective than low-potency steroids (in terms of severe pain, inflammation and swelling) (Roland 2007). Further investigation is required.

Evidence from one low quality trial (Masood 2008) suggests a glycerine-ichthammol medicated wick may provide better pain relief in early severe acute otitis externa than a triamcinolone/gramicidin/neomycin/nystatin medicated wick, but the magnitude or precision of effect has yet to be established.

The effectiveness of ear cleaning is unknown. The evidence for the efficacy of steroid-only drops is scant and has not been fully established. Further investigation is warranted in order to quantify the effects of both these interventions fully.

In general, given the apparent parity in clinical efficacy of topical interventions used to treat acute otitis externa, other factors such as cost, availability, dosing regimen, risk of contact sensitivity, risk of resistance and risk of ototoxicity may determine the choice of therapy. Parameters such as speed of healing and pain relief are yet to be determined for many topical treatments and may also influence this decision.

Patients prescribed antibiotic/steroid drops can expect their symptoms to last for approximately six days after treatment has begun. Patients are usually treated for seven to 10 days, although it is apparent that they are cured at different time points. It may be more useful when prescribing ear drops to instruct patients to use them for at least a week. If they have symptoms beyond the first week they should continue the drops until their symptoms resolve (and possibly for a few days after) for a maximum of a further seven days. Patients with symptoms beyond two weeks should be considered treatment failures and alternative management initiated.

Implications for research

Future trials should address a variety of general and more specific issues.

Adhering to the CONSORT statement improves the reporting of randomised controlled trials. Amongst other things it encourages the use of clear inclusion criteria, explicit randomisation schemes, full descriptions of drop-outs and withdrawals, and explicit reporting of adverse events. Use of confidence intervals is recommended in the CONSORT statement. A number of studies in this review used P values. The P value is limited in that it provides no information regarding the magnitude or precision of the result, and does not address how much the results would vary if the study were performed numerous times. It may indicate that a statistically significant result has been found, but in reality the difference could be so small as to be clinically meaningless.

Specifically, future trialists should attempt to address a clinically relevant hypothesis when designing a trial. Studies must state clearly their definition of acute otitis externa. Compliance should be closely monitored. Trialists should consider carefully how they handle bilateral disease in order to prevent a unit of analysis error. The use of additional outcome measures, such as time to recovery and pain relief, should be contemplated. Attempts should be made to perform intention-to-treat analyses. The cost-effectiveness of treatments, preferably through economic evaluations alongside clinical trials, would be valuable in guiding both clinical practice and health policy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cannon 1967

Methods	Randomised, double-blind trial comparing antibiotic/steroid ear drop with its vehicle (placebo)
Participants	Setting: private practice clinic Country: USA Age: 2 to 68 years Duration of treatment: 10 days Duration of follow up: 10 days Number randomised: 40 patients Inclusion criteria: otitis externa; nil else mentioned Exclusion criteria: not stated
Interventions	Methylprednisolone disodium phosphate (1.33 mg/ml) and neomycin sulphate (5 mg/ml) + 'vehicle' versus The 'vehicle'. The 'vehicle' comprised sodium citrate, sodium chloride, polysorbate 80, sodium bisulphite, phenethyl alcohol, benzalkonium chloride and sodium hydroxide. Dose: 4 drops 3 times daily Ear cleaning: performed on initial visit and again, if necessary, at day 5 and day 10 follow-up examinations Concurrent medication: not reported
Outcomes	1. Clinical resolution (good response)
Notes	No compliance monitoring Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Emgard 1999

Methods	Randomised, double-blind, multi-centre trial comparing a steroid ear drop with and without the use of an additional oral antihistamine
Participants	Setting: 3 hospital clinics Country: Sweden Age: 18 to 62 years Duration of treatment: 11 days

Emgard 1999 *(Continued)*

	Duration of follow up: 21 days Number randomised: 30 patients Inclusion criteria: patients with otitis externa Exclusion criteria: patients receiving oral corticosteroids within 30 days of the start of the study. Patients with known neoplasm, diabetes mellitus, multiple drug hypersensitivity, lactose intolerance, pregnant or breast-feeding women, those planning to become pregnant.
Interventions	0.5% betamethasone dipropionate (Diprosone®) + loratadine 20 mg od 10/7 versus 0.5% betamethasone dipropionate + oral placebo (no further details provided about this) Dose: ear drops; 4 drops 4 times daily for the first week, 4 drops once daily from day 8 to 11 Ear cleaning: use unclear; suction appears to have been used selectively for those with otorrhoea Concurrent medication: no oral corticosteroids within the preceding 30 days; no antibiotics or anti-inflammatory drugs allowed during the study; paracetamol permitted for pain
Outcomes	1. Clinical cure rate (resolution of signs - data evaluated; resolution of symptoms - a visual analogue scale was utilised)
Notes	The study was supported by a research grant from Schering-Plough who make both the ear drops and the oral antihistamine No compliance monitoring Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Freedman 1978

Methods	Randomised, double-blind trial comparing an antibiotic/steroid drop versus a placebo drop
Participants	Setting: hospital clinic Country: USA Age: 4 to 76 years Duration of treatment: 21 days Duration of follow up: 21 days Number randomised: 91 patients Inclusion criteria: patients with acute otitis externa Exclusion criteria: not stated
Interventions	Coly-Mycin S® (each ml contains colistin sulphate 3 mg + neomycin sulphate 3.3 mg + hydrocortisone acetate 10 mg (1%); thonzonium bromide 0.5 mg (0.05%), polysorbate '80', acetic acid and sodium acetate in a buffered vehicle; thimerosal 0.002% added as a preservative) versus Placebo (a starch solution with a turbidity matching that of the antibiotic drop) Dose: 4 drops 3 times daily Ear cleaning: performed at initial visit and days 3 and 7; a wick was inserted for the first 2 days

Freedman 1978 *(Continued)*

	Concurrent medication: at least 8 patients had other antibiotics or steroids (1 in active group; 7 in placebo group)
Outcomes	1. Clinical resolution (binary data not extractable as displayed graphically) 2. Microbial (effectiveness against pathogens used - not clinically relevant; furthermore, the data are not extractable)
Notes	No evaluable data; data displayed graphically and cannot be extracted No compliance monitoring Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Johnston 2006

Methods	Randomised, single-blind trial comparing acidifying agent spray versus acidifying agent/antibacterial/steroid spray
Participants	Setting: hospital clinic Country: UK Age: adults; nil further stated Duration of treatment: 2 weeks initially; if not cured at this stage a further 2 weeks of therapy was given Duration of follow up: 4 weeks Number randomised: 109 patients (53 with otitis externa; 56 with infected mastoid cavities) Inclusion criteria: adults with acute otitis externa or infected mastoid cavities Exclusion criteria: presence of cholesteatoma, aural polyps or congenital abnormalities; significant canal stenosis or false fundus either requiring a wick or systemic antibiotics; chronic otitis externa or acute exacerbation of chronic otitis externa and necrotising otitis externa. Other groups excluded were those with concomitant systemic disease, immunocompromised, under the age of 16, pregnant or contraindicated within formulary guidelines.
Interventions	2% glacial acetic acid (EarCalm®) versus 2% glacial acetic acid, 0.1% dexamethasone and 3250 U/ml neomycin sulphate (Otomize®) Dose: 1 puff 3 times a day Ear cleaning: performed on entry to the study; those with active disease at 2-week follow up underwent further aural toilet prior to continuing with the same therapy for a further 2 weeks Concurrent medication: excluded those requiring systemic antibiotics
Outcomes	1. Clinical resolution
Notes	Power calculation performed; 160 required in each arm; ethics committee required independent analysis part way through the study No compliance monitoring Quality score = C

Johnston 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Jones 1997

Methods	Two randomised, evaluator-blind, multi-centre trials comparing a quinolone antibiotic drop versus a non-quinolone antibiotic/steroid drop; 1 each in children and adults
Participants	Setting: 23 primary care and referral ambulatory care sites per trial Country: USA Age: mean age 39 years (adults) and 7 years (children) Duration of treatment: 10 days Duration of follow up: up to 20 days Number randomised: 601 patients (314 adults; 287 children) Inclusion criteria: unilateral or bilateral stable or exacerbating otitis externa of 2 weeks or less duration with purulent or mucopurulent otorrhoea, males, premenarchal females, women not of childbearing potential, women of childbearing potential with a negative urine pregnancy test and reliable contraception being practised Exclusion criteria: perforated ear drums within the previous 6 weeks, chronic otitis externa (duration greater than 2 weeks), seborrhoeic dermatitis of the pinna or ear canal, infection (fungal) known or suspected to be resistant to study drugs, invasive otitis externa requiring systemic antimicrobials, receipt of systemic/topical antimicrobials within the previous 14 days, receipt of systemic/topical quinolones within the previous 30 days, non-prescription therapy of otitis externa during previous 36 hours, long-term use of analgesic and/or anti-inflammatory therapy, undergoing cancer chemotherapy, known allergy to any component of the test medications, known compromised host resistance (e.g. immunocompromised; positive for HIV), known hepatitis, females under 12 years who reached menarche, female subjects who were pregnant or nursing, exposure to investigational agent within previous 90 days, previous enrolment in the current study, parent/guardian/subject unlikely to comply with protocol, disease/condition likely to impair evaluation of study drugs, high likelihood of death during study period. The only systematic exceptions to the exclusion criteria were allowance of topical antimicrobials for acne or analgesics and anti-inflammatory therapy if the dose had been stable for at least 14 days or 1 month respectively.
Interventions	Ofloxacin 0.3% 10 drops twice daily adults, 5 drops twice daily children versus Cortisporin® (neomycin + polymyxin B + hydrocortisone) 4 drops 4 times daily adults, 3 drops 4 times daily children Dose: see above Ear cleaning: not stated Concurrent medication: no systemic antimicrobials; no systemic or topical antimicrobials in preceding 14 days; no systemic or topical quinolones in preceding 30 days; no non-prescription therapy for otitis externa in preceding 36 hours; excluded long-term users of analgesics and/or anti-inflammatory drugs. Allowance of topical antimicrobials for acne or analgesic and anti-inflammatory therapy if the dose had been stable for at least 14 days or 1 month respectively.
Outcomes	1. Cure rate/clinical response (adults and children data were combined) 2. Combined clinical + microbial response in microbiologically evaluable subjects (adults' and children's data were combined) 3. Microbial eradication by subject (data not used as not deemed clinically pertinent)
Notes	2 of the authors worked for Daiichi Pharmaceutical Corporation who manufacture Ofloxacin. Also, overall clinical responses were assigned by the sponsors

Jones 1997 *(Continued)*

	Compliance was monitored Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Masood 2008

Methods	Randomised, single-blind trial comparing an antibiotic/steroid/anti-fungal ointment on dressing with an antiseptic/astringent solution on dressing in the initial treatment of severe acute otitis externa
Participants	Setting: Hospital ENT clinic Country: UK Age: adults (18 to 75 years) Duration of treatment: 48 hours Duration of follow up: Until resolution (not explicitly stated by authors) Number randomised: 64 patients Inclusion criteria: adults with severe acute otitis externa for less than 3 weeks Exclusion criteria: recurrent chronic otitis externa, co-existing middle-ear pathology, those requiring topical/systemic antibiotics within the past 3 weeks, possible or known drug sensitivity to agents used
Interventions	10% glycerine-ichthammol (GI) solution on ribbon gauze versus Triadcortyl® ointment on ribbon gauze (triamcinolone acetonide 0.1%, gramicidin 0.025%, neomycin sulphate 0.25%, nystatin 100,000 units/g) Dose: medicated dressing inserted into ear canal for 48 hours Ear cleaning: at initial visit Concurrent medication: nil mentioned
Outcomes	1. Pain score 2. Signs score
Notes	Compliance monitoring: as the medicated dressing remained within the ear canal for 48 hours patient compliance was not an issue Quality score = B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	

Mosges 2007

Methods	Randomised, double-blind trial comparing an antibiotic ointment with steroid versus the antibiotic ointment alone

Mosges 2007 *(Continued)*

Participants	Setting: 11 ENT specialist practices Country: Germany Age: adults (> or = 18 years old) mean = 51.7 years Duration of treatment: 10 days Duration of follow up: 10 days (range 9 to 11 days) Number randomised: 152 patients Inclusion criteria: adults with acute otitis externa Exclusion criteria: known viral, fungal or tuberculous ear infections, otitis media, mastoiditis, mastoid cavities, stenosis, exostosis, cholesteatoma, perforated tympanum, invasive malignant otitis externa, pretreatment of the current otitis externa with antibiotics or corticosteroids, diabetes, use of immunosuppressants, the need for systemic antibiotic or corticoid treatment, or the possible use of analgesics other than paracetamol during the study
Interventions	Polymyxin B sulfate (7500 IU) + bacitracin (300 IU) (an antibiotic) + hydrocortisone acetate (10 mg/g) ointment (Polyspectran HC® Salbe) versus Polymyxin B sulfate (7500 IU) + bacitracin (300 IU) ointment Dose: medicated gauze strip inserted on day 0 and removed by patient after 24 hours. Then ointment applied twice daily. Then medicated gauze strip inserted on day 3 to 5 and removed 24 hours later by the patient. Then ointment applied twice daily. Ear cleaning: not mentioned Concurrent medication: only paracetamol was permitted
Outcomes	1. Clinical symptom score reduction 2. Subscore mean reduction 3. Pain score (VAS) reduction 4. Paracetamol consumption 5. Efficacy/tolerability rating (by patient and investigator)
Notes	Compliance monitoring was performed: the 5 g ointment tubes were weighed after 10 days; equivalent amounts in each group had been used Quality score = B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mosges 2008

Methods	Randomised, double-blind trial evaluating the addition of a steroid to an antibiotic drop
Participants	Setting: 21 ENT specialist practices Country: Germany Age: 18 to 76 years Duration of treatment: 10 days Duration of follow up: 10 +/- 2 days Number randomised: 338 patients Inclusion criteria: adults with a diagnosis of acute unilateral bacterial otitis externa and a previous episode of otitis externa within the last 2 months Exclusion criteria: otitis externa from viral, fungal or tubercular agents, otitis media, mastoiditis, mastoid cavities, stenosis, exostosis, cholesteatoma, perforated tympanic membrane, invasive malignant chronic otitis externa, (pre-) treatment with local/systemic antibiotics or corticoids, use of analgesics

Mosges 2008 *(Continued)*

	or NSAIDs other than paracetamol, diabetes mellitus, application of immunosuppressants, vaccination reactions, intolerance/hypersensitivity to one of the study drugs or paracetamol, severe hepatic or renal insufficiencies, alcohol abuse, existing or intended pregnancy, lactation, well-founded doubt about the patients co-operation, participation in another clinical trial or previous participation in this trial.
Interventions	Polymyxin B sulfate 7500 IU + neomycin sulfate 3500 IU versus Dexamethasone sodium phosphate 0.132% + polymyxin B sulfate 7500 IU + neomycin sulfate 3500 IU Dose: 2 drops 3 times daily Ear cleaning: not mentioned Concurrent medication: use of paracetamol was permitted
Outcomes	1. Change in Clinical Symptom Score (CSS) 2. Change in individual subscores 3. Change in VAS (visual analogue score) 4. Use of paracetamol 5. Patients global assessment of efficacy 6. Complete clinical cure (CSS = 0) at final visit
Notes	Compliance monitoring not performed. The study was funded by an unrestricted grant from Alcon Pharma Germany GmbH. One author has served as a scientific advisor to Alcon Pharma who manufacture dexamethasone/polymyxin B/neomycin sulfate (Dexa-Polyspectran). Only unilateral cases were included Quality score = A

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	The medication was fitted in identical plastic bottles and the labelling was masked by using the study code and the randomisation number

Neher 2004

Methods	Randomised, double-blind trial comparing an endogenous antiseptic drop versus a antibiotic/steroid drop
Participants	Setting: hospital clinic Country: Austria Age: 8 to 89 years Duration of treatment: until cure (9 days in vast majority of cases) Duration of follow up: unclear (until cure?) Number randomised: 50 patients Inclusion criteria: patients with acute otitis externa (diagnosed by an ENT doctor at the outpatient department) Exclusion criteria: malignant otitis externa, topical treatment with other agents, systemic application of antibiotics or corticoids, pregnancy, and participation in another study at the same time
Interventions	2 ml 1% NCT (N-chlorotaurine) once daily versus

Neher 2004 *(Continued)*

	1 ml Otosporin® (1.27 mg polymyxin B sulphate + 5 mg neomycin sulphate + 10 mg hydrocortisone per ml) once daily Dose: see above Ear cleaning: not stated. The substances were applied to the outer ear canal using a rolled cotton wick soaked with the agent. This ear wick was left in place and was changed daily. Concurrent medication: excluded those on topical treatment with other agents, those on systemic antibiotics or corticoids
Outcomes	1. Time to healing (WMD) 2. Pain scores (data not extractable; the means from day 1 to 5 can be subtracted but SDs cannot) 3. Cure rate (available for days 1 through 9; we used the cure rates given at day 9)
Notes	Compliance monitoring not performed Study was supported by the Austrian Science Fund and the Jubilee Research Fund of the Austrian National Bank Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Olivera 2004

Methods	Randomised, double-blind trial comparing glycerin and aqueous solutions of ototopical ciprofloxacin
Participants	Setting: hospital clinic Country: Argentina Age: 8 to 89 years Duration of treatment: 7 days Duration of follow up: 7 days Number randomised: 33 patients Inclusion criteria: acute otitis externa manifested as drainage, swelling, pain, and/or erythema in the external ear canal. Bacteriologic confirmation of infection. An ability to follow investigator's instructions. Exclusion criteria: allergy or contraindication to quinolones. The need to start an incompatible treatment during the study period. Chronic illness requiring long-term pharmacologic therapy. Participation in another clinical trial during the previous 15 days.
Interventions	0.3% ciprofloxacin glycerin solution versus 0.3% ciprofloxacin aqueous solution Dose: 3 drops twice daily Ear cleaning: not mentioned Concurrent medication: excluded patients that needed to start an incompatible treatment during the study period, and those requiring long-term pharmacotherapy for a chronic illness
Outcomes	1. Cure rate

Olivera 2004 *(Continued)*

Notes	They report a greater resolution of discharge/otorrhoea in the glycerin group compared with the aqueous group (glycerin group: 17/18 had otorrhoea at visit 1, compared with 2/18 with otorrhoea at visit 2; versus the aqueous group: 12/15 had otorrhoea at visit 1, compared with 4/15 with otorrhoea at visit 2; reported as being statistically significant (although numbers are small and so interpretation should be cautious). Full compliance but method of monitoring not stated Quality score = A

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Roland 2004

Methods	Randomised, evaluator-blind, multi-centre trial comparing a quinolone antibiotic/steroid versus a non-quinolone antibiotic/steroid drop
Participants	Setting: 23 clinical centres Country: USA Age: 1 to 90 years Duration of treatment: 7 days Duration of follow up: 18 days Number randomised: 468 patients Inclusion criteria: patients 1 year and over with a clinical diagnosis of mild, moderate or severe acute otitis externa of less than 4 weeks duration in 1 or both ears and intact ear drums Exclusion criteria: acute or chronic otitis media, post-tympanostomy tube acute otorrhoea, malignant otitis externa, overt fungal or viral ear infections, congenital abnormalities of the ear canal, obstructive bony exostoses, mastoid or other suppurative non-infectious ear disorders, seborrhoeic dermatitis of the ear canal, a current or prior history of immunosuppressive disorders, acute or chronic renal insufficiency, hepatitis, diabetes mellitus, pregnancy, lactation
Interventions	Ciprodex® (0.3% ciprofloxacin + 0.1% dexamethasone) (3 drops twice daily for children, 4 drops twice daily for 12 years and over) versus Cortisporin® (neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1.0%) (3 drops 3 times daily for children, 4 drops 3 times daily for 12 years and over) Dose: see above Ear cleaning: at initial visit and at follow-up visits if needed Concurrent medication: wash-out period required prior to commencing the study; 3 days for short-acting antibiotics or 7 days for long-acting antibiotics. Systemic or otic corticosteroids, topical treatment with alcohol, vinegar or other astringent medication, systemic antimicrobial therapy, non-steroidal or other inflammatory drugs was not permitted. Analgesic use was restricted to acetaminophen with or without codeine.
Outcomes	1. Cure rate 2. Microbial cure
Notes	The study was supported by a grant from Alcon Research Ltd who make Ciprodex® Investigators attended a training session prior to initiation of the study to ensure consistency of grading scores

Roland 2004 *(Continued)*

	The most recent investigators assessment scores were carried forward for patients who missed follow-up visits 468 randomised (ITT population); 396 culture-positive for bacteria at baseline/day 1 (modified ITT population) Compliance monitoring performed Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Roland 2007

Methods	Randomised single-blind trial comparing a quinolone antibiotic/steroid versus a non-quinolone antibiotic/steroid for otitis externa pain
Participants	Setting: unclear (multi-centre) Country: USA Age: 1 years of age and over Duration of treatment: 7 days Duration of follow up: 18 days Number randomised: 524 patients assessed Inclusion criteria: patients 1 year and over with a clinical diagnosis of moderate (constant but tolerable pain) or severe (intense and unrelenting pain) acute otitis externa of less than 4 weeks duration in 1 or both ears and intact tympanic membranes Exclusion criteria: clinically diagnosed chronic suppurative otitis media, acute otitis media, acute otorrhoea, clinically diagnosed malignant otitis externa, overt fungal or viral infection, congenital abnormalities of the external auditory canal, mastoiditis or other suppurative non-infectious ear disorders, malignant tumour of the external auditory canal, prior history of otologic surgery (except surgery confined to the temporomandibular joint), immunosuppressive disorders, current or prior use of systemic (within 30 days) or topical (7 days) steroids, infection requiring systemic antibiotics, current use of topical or oral antibiotics or analgesics (except acetaminophen) or treatment with alcohol, vinegar, or other astringents, known sensitivity to any study medication, or pregnancy or lactation
Interventions	Ciprofloxacin 0.3% + dexamethasone 0.1% (3 drops twice daily (adults); 4 drops twice daily (children)) versus Neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1.0% (3 drops 3 times daily (adults); 4 drops 3 times daily (children)) Dose: see above Ear cleaning: nil mentioned. For patients who required a pope wick, or something similar, the first dose only was doubled (nil further stated in terms of numbers of patients requiring this). Concurrent medication: use of acetaminophen and codeine permitted
Outcomes	1. Patient reported pain 2. Investigator assessment of inflammation, oedema, tenderness and discharge 3. Analgesic use
Notes	One of the authors of the study works for Alcon Research Ltd who make Cip/Dex Compliance monitoring performed

Roland 2007 *(Continued)*

Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Only the designated individual assigned to dispense the test article had access to the specific dosing regimen and provided instructions to patients

Roland 2008

Methods	Randomised, single-blind trial comparing a (quinolone) antibiotic/steroid drop with a (non-quinolone) antibiotic/steroid drop plus oral antibiotic
Participants	Setting: unclear (multi-centre: 21 investigators) Country: USA Age: 1 year of age and over Duration of treatment: 7 days ((quinolone)antibiotic/steroid drop); or 10 days (non-quinolone) antibiotic/steroid drop plus oral antibiotic Duration of follow up: 14 to 17 days ((quinolone)antibiotic/steroid drop); or 17 to 20 days ((non-quinolone) antibiotic/steroid drop plus oral antibiotic) Number randomised: 206 patients Inclusion criteria: 1 year of age and over, had a diagnosis of mild, moderate or severe acute otitis externa, severity of symptoms at least "mild". Acute otitis externa symptoms present for longer than 2 days. Patients to refrain from water immersion of the ear during the study. Informed consent given. Agreement to comply with protocol requirements Exclusion criteria: acute otitis externa symptoms present for 2 days or less; non-intact tympanic membrane, with or without otorrhoea. Acute otitis media, malignant otitis externa, chronic suppurative otitis media, mastoiditis, seborrheic dermatitis of the external auditory canal, or other suppurative non-infectious ear disorders. Known or suspected fungal, viral or mycobacterium ear infections. Diabetes, immunosuppressive disorders, renal abuse, hepatitis, mononucleosis, chronic diarrhoea, narcotic abuse. Concomitant use of ear washes, systemic antibiotic agents, steroids, analgesics other than acetaminophen, and any preparation that might obscure study results. Known or suspected allergy to any component of study medications
Interventions	Ciprofloxacin 0.2% + hydrocortisone 1% (3 drops twice daily x 7 days) versus Neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1% (adults: 4 drops 3 times daily + up to 500 mg amoxicillin 3 times daily for 10 days; children: 3 drops 3 times daily + 40 mg/kg/day in 3 divided doses for 10 days) Dose: see above Ear cleaning: at entry the infected ear(s) was cleansed of fluid + debris using lavage, dry mop or suction Concurrent medication: use of acetaminophen permitted
Outcomes	1. Investigator assessment of response (clinical-microbiological) 2. Microbiological cure 3. Time to end of ear pain 4. Investigator assessment of tenderness and otalgia
Notes	Compliance monitoring not performed. End-of-therapy (EOT) and test-of-cure (TOC) visits differ for each group

Roland 2008 *(Continued)*

	Authors are employees, stockholders or consultants of Alcon. Alcon provided financial support to 3 authors to participate as principle investigators on this trial. The research was supported by institutional grants to each investigator from Alcon Research Ltd. Quality score = B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Strict avoidance of discussions among staff members that might reveal treatment assignments was mandated by the protocol

Sabater 1996

Methods	Randomised, double-blind trial comparing a quinolone-antibiotic drop versus an aminoglycoside-antibiotic drop
Participants	Setting: hospital clinic Country: Spain Age: adults Duration of treatment: 8 days Duration of follow up: 8 days (diffuse otitis externa group); 30 days (chronic suppurative otitis media group) Number randomised: 101 patients (54 patients with diffuse otitis externa; 47 patients with chronic suppurative otitis media) Inclusion criteria: patients with diffuse otitis externa and chronic suppurative otitis media Exclusion criteria: patients under 18 years of age, pregnant or lactating women, allergies to the drugs used in the study, severe renal or liver failure, patients treated with antibiotics within 7 days of entering the study, or patients with chronic suppurative otitis media who had hearing loss greater than 60 dB
Interventions	0.5% ciprofloxacin versus 0.3% gentamicin Dose: 5 drops 3 times daily Ear cleaning: not mentioned Concurrent medication: no antibiotics in the preceding 7 days
Outcomes	1. Clinical cure
Notes	Article translated from Spanish Cures given in % but need actual numbers (author emailed and subsequently replied and quality score upgraded to B) Not matched for severity on entry (there were more severe cases in the ciprofloxacin group); no other details provided on demographics or matching No compliance monitoring Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Schwartz 2006

Methods	Randomised, multi-centre, parallel group, evaluator-blind trial comparing once daily Floxin® (ofloxacin) with 4 times daily Cortisporin® (neomycin/polymyxin B/hydrocortisone) in paediatric patients
Participants	Setting: 34 investigative centres Country: USA Age: 2 to 12 years (clinically evaluable patients) Duration of treatment: 7 to 10 days Duration of follow up: 14 to 19 days Number randomised: 278 patients Inclusion criteria: paediatric patients greater than or equal to 6 months and less than or equal to 12 years of age with stable or exacerbating symptoms of otitis externa of less than 2 weeks duration with otitis externa of presumed bacterial origin. The presence in 1 or both ears of scores greater than or equal to 2 for oedema and tenderness, a score of greater than or equal to 1 or erythema (0 = none, 1 = mild, 2 = moderate, 3 = severe) and a score greater than or equal to 1 for ear secretion/exudates (0 = none, 1 = serous, 2 = mucopurulent, 3 = purulent). The sum of all scores required for enrolment was greater than or equal to 6. Exclusion criteria: the presence of a perforated tympanic membrane in the preceding 6 months; chronic otitis externa (current episode greater than or equal to 2 weeks); seborrhoeic dermatitis in the external ear canal or pinna; invasive otitis externa requiring systemic antibiotics; therapy in the preceding 7 days with systemic or topical antibiotics, steroids, or non-steroidal anti-inflammatory drugs; over-the-counter therapy in the preceding 36 hours; known or suspected allergy to quinolones or any ingredients of the test medications; and infection suspected to be resistant to the study drugs
Interventions	0.3 % ofloxacin otic solution (Floxin®) 5 drops once daily versus Cortisporin® (polymyxin B 10,000 U/ml; neomycin sulphate 3.5 mg/ml; hydrocortisone 10.0 mg/ml) 3 drops 4 times daily Dose: see above Ear cleaning: not mentioned (presumably not performed as this is a paediatric study) Concurrent medication: no systemic or topical antibiotics, steroids or non-steroidal anti-inflammatory drugs in the preceding 7 days. No over-the-counter therapy in the preceding 36 hours. No medications were permitted during the study except at the discretion of the investigator (e.g. topical acne medication or chronic pain medications, including steroidal and non-steroidal ant-inflammatory drugs, with no change in dose during the entire study were permitted).
Outcomes	1. Clinical response (i) Investigator-determined (ii) Sponsor-determined 2. Clinical-microbiological response (in microbiologically evaluable patients) 3. Pain scores (VAS, from parent/guardian diaries) 4. Adverse events (table given, P values calculated using Fisher's exact test)
Notes	Trial funded by Daiichi Pharmaceutical Corporation (manufacturers of Floxin®); the sponsors blinded assessments of clinical cure with regard to their product were slightly more conservative than the investigator assessments. However, to reduce the potential risk of bias the sponsor assessment was not utilised. Furthermore, it was only available at one time-point (day 14 to 19) whereas the investigator assessment was performed at day 7 to 9 and day 14 to 19. Compliance monitoring performed Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement

Schwartz 2006 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Slack 1987

Methods	Randomised, double-blind trial comparing an antiseptic versus antibiotic/steroid versus antibiotic/steroid/antifungal ear drops
Participants	Setting: hospital clinic Country: UK Age: not stated Duration of treatment: until cure Duration of follow up: until cure Number randomised: 28 patients Inclusion criteria: patients with otitis externa in whom no treatment had been given for at least 2 weeks Exclusion criteria: previous mastoid surgery and visible perforated ear drum
Interventions	Boric acid 4% (with absolute alcohol 25% + sterile water to 100%) versus Otosporin® (polymyxin B sulphate 10,000 units/ml; neomycin sulphate 0.5%; hydrocortisone 1%) versus Polymyxin B sulphate 15,000 units/ml + flucinolone acetonide 0.1% + econazole 1% + methanol 5% + glycerol 10% + polyethylene glycol '300' to 100% Dose: 2 drops 4 times daily Ear cleaning: performed at initial visit and weekly thereafter Concurrent medication: not reported
Outcomes	1. Cure rate
Notes	No matching at entry (boric acid group had higher severity scores at entry). No compliance monitoring. Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tsikoudas 2002

Methods	Randomised, double-blind trial comparing ototopical antibiotic/steroid drops versus the steroid-only version
Participants	Setting: hospital clinic Country: UK Age: adults Duration of treatment: 14 days Duration of follow up: 11 days Number randomised: 39 patients Inclusion criteria: adults with otitis externa

Tsikoudas 2002 *(Continued)*

	Exclusion criteria: age less than 18 years, neomycin allergy, ear canal oedema severe enough to prevent the use of topical ear drops, concurrent middle ear disease, patients requesting exclusion
Interventions	Vista-Methasone N® (betamethasone sodium phosphate 0.1% + neomycin sulphate 0.5%) versus Vista-Methasone® (betamethasone sodium phosphate 0.1%) Dose: not stated Ear cleaning: performed at initial visit Concurrent medication: not reported
Outcomes	1. Clinical: patient and observer assessments
Notes	Results in separate table. Matching at entry for severity only. Compliance was monitored, with no difference between the 2 groups Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

van Balen 2003

Methods	Randomised, double-blind, multi-centre trial comparing antiseptic versus antiseptic/steroid versus steroid/antibiotic ear drops in primary care
Participants	Setting: 79 general practices Country: Netherlands Age: mean 43.6 years Duration of treatment: up to 21 days Duration of follow up: 42 days Number randomised: 213 patients Inclusion criteria: patients with signs and symptoms of acute otitis externa Exclusion criteria: age 17 years or younger, pregnancy, chronic otitis externa (more than 3 weeks), a furuncle in the external auditory canal, acute otitis media, a perforated ear drum, perichondritis, fever, allergy to any of the study drops, having already been recruited to the study or been treated for acute otitis externa in the past month
Interventions	Acetic acid versus Acetic acid + steroid (0.1% triamcinolone acetonide) versus Steroid + antibiotic (0.66 mg dexamethasone phosphate sodium; 5 mg neomycin sulphate; 10,000 IU polymyxin B sulphate per ml) Dose: 3 drops 3 times daily Ear cleaning: performed on initial visit. Wick inserted for 24 hours if ear canal was swollen and repeated as necessary. Concurrent medication: not reported
Outcomes	1. Cure rate

van Balen 2003 *(Continued)*

	2. Time to recovery/healing (plotted in a separate table) 3. Recurrence rate
Notes	Author emailed to check that the study reported in Huisarts en Wetenschap (Dutch General Practice Journal) is the same data: later confirmed by author Compliance monitoring performed Funding from the Fund for Common Disorders from the Dutch College of General Practitioners and Foundation for the Advancement of Appropriate Drug Usage in the Central Region of the Netherlands Quality score = A

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wadsten 1985

Methods	Randomised , evaluator-blind trial comparing 2 antibiotic/steroid ear drops
Participants	Setting: hospital clinic Country: Sweden Age: 6 to 76 years Duration of treatment: 7 days Duration of follow up: 14 days Number randomised: 64 patients Inclusion criteria: patients with acute otitis externa Exclusion criteria: recent treatment for external otitis, fever, perichondritis or perforated ear drums
Interventions	Sofradex® (framycetin, gramicidin, dexamethasone) versus Terra-Cortril® with polymyxin B (TPB) (oxytetracycline, polymyxin B, hydrocortisone) Dose: 3 to 5 ear drops 3 to 4 times daily Ear cleaning: performed on initial visit. Wick inserted for 24 hours if ear canal was swollen Concurrent medication: oral salicylates and indomethacin were given to those experiencing acute pain and tenderness
Outcomes	1. Patient and observer assessments (blockage, pain, discharge, itching on a 10 cm linear analogue scale)
Notes	No details on matching at entry. No compliance monitoring. Quality score = C

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

bd = twice a day

IU = international unit
NCT = N-chlorotaurine
od = once a day
SD = standard deviation
tds = three times a day
TP = trimethoprim + polymyxin B
TPB = polymyxin B
TSP = trimethoprim + polymyxin B + sulfacetamide
VAS = visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abelardo 2009	ALLOCATION Randomised PARTICIPANTS 45 patients with otitis externa (11 patients had bilateral disease) INTERVENTIONS Betamethasone versus betamethasone/neomycin OUTCOMES The primary efficacy analysis of median symptom score at day 15 and median percentage change in symptom score at day 15 was analysed at ear level With regard to the data reported at patient level ("number of patients showing an improvement in symptoms"), there is insufficient description of the outcome measure in the text of the article. It appears to be based on patients' subjective descriptions of whether they felt better or worse on treatment rather than a more robust objective assessment.
Akroyd 1959	ALLOCATION Participants were not randomised
Anonymous 1967	ALLOCATION Participants were divided into 2 groups, but allocation not described as randomised
Arnes 1993	ALLOCATION This was an open/non-blinded trial
Baba 1986	ALLOCATION Participants were not randomised
Baba 1995	ALLOCATION Participants were not randomised (article in Japanese)
Bain 1976	ALLOCATION Randomised PARTICIPANTS Study included participants with acute and chronic otitis externa, but the data on the acute group were not extractable
Bak 1983	ALLOCATION Quasi-randomised (first 54 allocated to one group, the next 31 to the other group)
Barr 1991	ALLOCATION Quasi-randomised (according to date of birth)

Study	Reason for exclusion
Barton 1979	ALLOCATION Randomised PARTICIPANTS Study included participants with bilateral ear disease and reported results at ear level only
Buch-Rasmussen 1979	ALLOCATION Randomised PARTICIPANTS Study evaluated participants with eczematous otitis externa
Cannon 1970	ALLOCATION Randomised PARTICIPANTS 10 patients (23%) had otitis externa secondary to otitis media and 2 patients had seborrhoea. The acute otitis externa data was not extractable.
Cassisi 1977	ALLOCATION Quasi-randomised (alternation)
Clayton 1990	ALLOCATION Randomised PARTICIPANTS Study included participants with chronic otitis externa, mastoid cavity infections and central perforations. The acute otitis externa data were not extractable.
Dadagian 1974	ALLOCATION Randomised PARTICIPANTS Study included participants with bilateral ear disease and reported results at ear level only
Durcan 1968	ALLOCATION Participants were not randomised
Emgard 2005	ALLOCATION This was an open/non-blinded trial
Federspil 1983	ALLOCATION Double-blind randomised trial PARTICIPANTS 42 patients with acute or recurrent ENT infections. The acute otitis externa data were not extractable.
Ghilardi 1985	ALLOCATION Participants were not randomised
Goldenberg 2002	ALLOCATION This was an open/non-blinded trial
Gordana 2007	ALLOCATION Randomised PARTICIPANTS 98 patients with acute otitis externa

Study	Reason for exclusion
	INTERVENTIONS Castellani tintura rubra versus dexamethasone-neomycin solution OUTCOMES This was an abstract; there is insufficient detail regarding the study and its outcomes
Gyde 1978	ALLOCATION Double-blind, randomised PARTICIPANTS Study evaluated participants with otorrhoea secondary to otitis externa, recurrent otitis media with tympanic membrane perforation, mastoid cavity infections and postoperative infections. The acute otitis externa data were not extractable.
Gyde 1981	ALLOCATION Randomised PARTICIPANTS Study evaluated participants with otorrhoea secondary to otitis externa, recurrent otitis media with tympanic membrane perforation, mastoid cavity infections and postoperative infections. The acute otitis externa data were not extractable.
Gyde 1982	ALLOCATION Randomised PARTICIPANTS Study evaluated participants with otorrhoea secondary to otitis externa, recurrent otitis media with tympanic membrane perforation, mastoid cavity infections and postoperative infections. The acute otitis externa data were not extractable.
Hicks 1983	ALLOCATION Randomised PARTICIPANTS 26 patients with otitis externa INTERVENTIONS Multiple topical medications were used with no data relating to individual outcomes
Hornigold 2008	ALLOCATION This was an open/non-blinded trial
Jacobsson 1991	ALLOCATION Randomised PARTICIPANTS Study evaluated participants with eczematous otitis externa
Joachims 1983	ALLOCATION Participants were not randomised
Joachims 1984	ALLOCATION Participants were not randomised (article in Hebrew)
Kantas 2007	ALLOCATION Randomised PARTICIPANTS 264 patients with acute otitis externa

Study	Reason for exclusion
	INTERVENTION Multiple interventions used in each arm: For the 5% trichloroacetic acid (TCA) group: instilled so that it was covering the tympanic membrane and filling the outer ear canal for a period of 10 to 15 seconds. The ear was then suctioned dry and then washed with 3% boric acid aqueous solution under microscopic control. In severe cases, a ribbon gauze soaked in 3% boric acid +/- antifungal drops was inserted for 3 days. After gauze removal the antifungal drops continued for 7 further days. For oedematous canals, additional 20% to 30% TCA instilled through gentle circular movements, facilitated by a cotton applicator. 17 tympanic membrane granulomas required repeated cauterisation with 20% to 30% TCA to a cotton applicator. Additional antibiotic was given to those severe cases with pinna cellulitis. For the polymyxin B/neomycin/fluocinolone (Synalar®) group: number of drops not stated. Drops applied 3 times daily for 10 days. Severe cases ribbon gauze soaked with Synalar was inserted into the canal and removed after 3 days.
Kime 1978	ALLOCATION Randomised PARTICIPANTS Study included participants with bilateral ear disease and reported results at ear level only
Lafuma 2002	ALLOCATION Study evaluating cost-effectiveness of 2 treatments based on data from 2 previous RCTs
Lambert 1981	ALLOCATION Open/non-blinded trial
Leigh 1966	ALLOCATION Participants were not randomised
Lopes 1991	ALLOCATION Randomised (article in Portuguese) PARTICIPANTS 43 patients with ENT infections (otitis externa, acute pharyngitis, acute tonsillitis, acute sinusitis, acute laryngitis, acute otitis media). The acute otitis externa data were not extractable.
Margarino 2002	ALLOCATION This was an open/non-blinded study (article in Italian)
Marks 1968	ALLOCATION Participants were not randomised
Nakamura 1972	ALLOCATION Participants were not randomised
Neuss 1963	ALLOCATION Participants were not randomised (article in German)
Ordonez 1978	ALLOCATION Randomised PARTICIPANTS Study included participants with bilateral ear disease and reported results at ear level only
Pedersen 1971	ALLOCATION Randomised, double-blind (article in Danish)

Study	Reason for exclusion
	PARTICIPANTS 37 patients with acute diffuse otitis externa, eczematous otitis externa, furunculosis or otomycosis. The acute otitis externa data were not extractable.
Pistorius 1999	ALLOCATION This was an open/non-blinded study
Pond 2002	ALLOCATION Randomised PARTICIPANTS 94 patients with acute otitis externa INTERVENTION Intervention groups used a variety of topical treatments. Some patients also had oral antibiotics and intramuscular steroids.
Psifidis 2005	ALLOCATION This was an open/non-blinded study
Radjenovic 2007	ALLOCATION Randomised PARTICIPANTS 98 patients with acute otitis externa INTERVENTION Castellani tintura rubra versus dexamethasone neomycin solution OUTCOMES This was an abstract; insufficient data extractable
Rajkumar 2005	ALLOCATION Randomised PARTICIPANTS 42 patients with otitis externa INTERVENTION Betamethasone versus betamethasone plus neomycin drops OUTCOMES This was an abstract. No extractable data (mean pre and post-treatment visual analogue scores for both arms are provided, but no details on numbers in each arm and the standard deviations). These data were subsequently published in full by one of the co-authors but this study was excluded from this review (see Abelardo 2009).
Rubin 1958	ALLOCATION Randomised PARTICIPANTS 268 patients with diffuse eczematoid external otitis, external otitis secondary to surgery, suppurative acute otitis media, suppurative chronic otitis media
Ruth 1990	ALLOCATION Randomised PARTICIPANTS 53 patients with acute otitis externa INTERVENTION

Study	Reason for exclusion
	Patients in either intervention group with swollen canals had 0.1% aluminium acetotartrate wicks inserted for 24 hours. This antiseptic may have influenced the outcome of this trial. No details were provided on the numbers of participants involved, the number in each group or their individual outcomes.
Senturia 1973	ALLOCATION Participants were not randomised
Smith 1990a	ALLOCATION This was an open/non-blinded trial
Smith 1990b	ALLOCATION This was an open/non-blinded trial
Stride 1962a	ALLOCATION Participants were not randomised
Stride 1962b	ALLOCATION Participants were not randomised
Supiyaphun 1995	ALLOCATION Participants were not randomised
Torun 2004	ALLOCATION Participants were not randomised
van Hasselt 2004	ALLOCATION Randomised PARTICIPANTS Study included participants with bilateral ear disease and reported results at ear level only
Vinther 1993	ALLOCATION Randomised PARTICIPANTS Study evaluated participants with eczematous otitis externa
Wilde 1995	ALLOCATION Randomised PARTICIPANTS 70 patients with otitis externa and chronic suppurative otitis media; acute otitis externa data were not extractable
Worgan 1969	ALLOCATION Randomised, double-blind PARTICIPANTS 76 ears with acute and chronic otitis externa. All 6 cases of acute otitis externa fell into 1 intervention group.
Yaniv 2002	ALLOCATION This was an open/non-blinded study
Yelland 1993	ALLOCATION Randomised PARTICIPANTS

Study	Reason for exclusion
	Study included participants with bilateral ear disease and reported results at ear level only

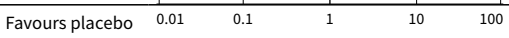
DATA AND ANALYSES

Comparison 1. Topical: antibiotic/steroid vs placebo (neomycin + methylprednisolone vs vehicle)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical resolution ("good" response): day 5 or day 10 (? - unclear)	1	40	Odds Ratio (M-H, Fixed, 95% CI)	11.0 [2.00, 60.57]

Analysis 1.1. Comparison 1 Topical: antibiotic/steroid vs placebo (neomycin + methylprednisolone vs vehicle), Outcome 1 Clinical resolution ("good" response): day 5 or day 10 (? - unclear).

Study or subgroup	Antibiotic/steroid n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Cannon 1967	11/20	2/20		100%	11[2,60.57]
Total (95% CI)	**20**	**20**		**100%**	**11[2,60.57]**
Total events: 11 (Antibiotic/steroid), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.75(P=0.01)					

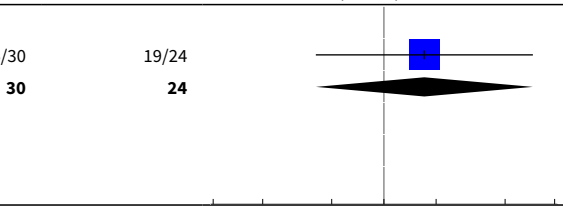


Comparison 2. Topical: quinolone antibiotic vs non-quinolone antibiotic (ciprofloxacin vs gentamicin)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical cure at 7 to 9 days	1	54	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.40, 7.23]

Analysis 2.1. Comparison 2 Topical: quinolone antibiotic vs non-quinolone antibiotic (ciprofloxacin vs gentamicin), Outcome 1 Clinical cure.

Study or subgroup	Quinolone n/N	Non-quinolone n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Clinical cure at 7 to 9 days					
Sabater 1996	26/30	19/24		100%	1.71[0.4,7.23]
Subtotal (95% CI)	**30**	**24**		**100%**	**1.71[0.4,7.23]**
Total events: 26 (Quinolone), 19 (Non-quinolone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					

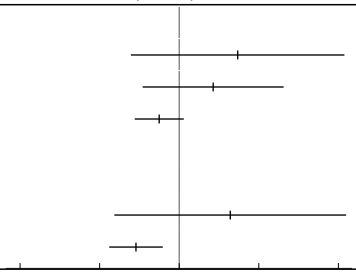


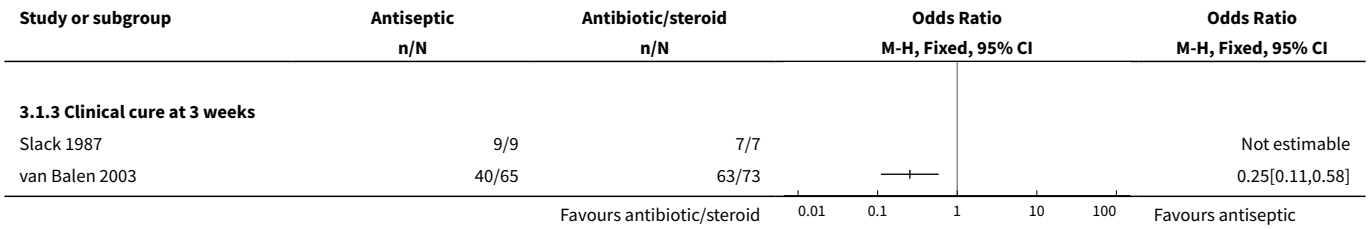
Comparison 3. Topical: antibiotic/steroid vs antiseptic (Neher 2004: polymyxin B + neomycin + hydrocortisone vs N-chlorotaurine; Slack 1987: polymyxin B + neomycin + hydrocortisone vs boric acid; van Balen 2003: polymyxin B + neomycin + dexamethasone vs acetic acid)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical cure	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Clinical cure at 7 to 9 days	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Clinical cure at 2 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Clinical cure at 3 weeks	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Recurrence between 3 and 6 weeks	1	115	Odds Ratio (M-H, Fixed, 95% CI)	3.12 [1.37, 7.09]
3 Time to healing (days)	1	50	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-2.69, -0.91]

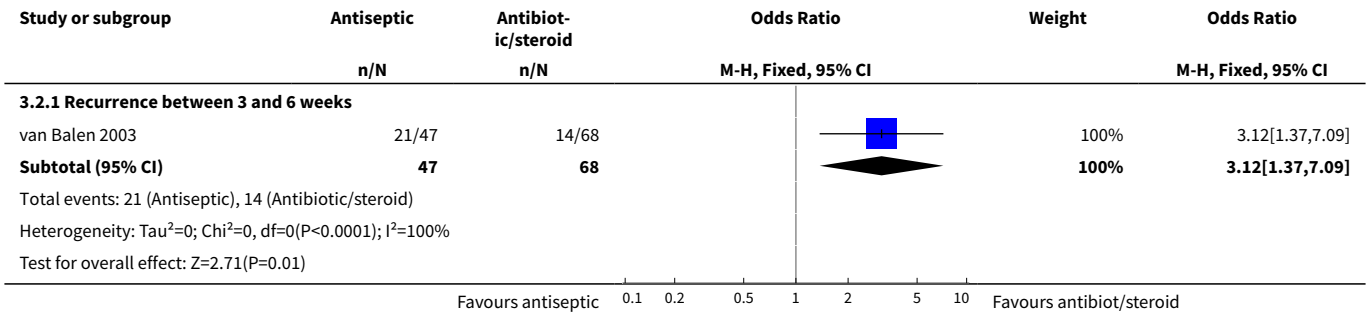
Analysis 3.1. Comparison 3 Topical: antibiotic/steroid vs antiseptic (Neher 2004: polymyxin B + neomycin + hydrocortisone vs N-chlorotaurine; Slack 1987: polymyxin B + neomycin + hydrocortisone vs boric acid; van Balen 2003: polymyxin B + neomycin + dexamethasone vs acetic acid), Outcome 1 Clinical cure.

Study or subgroup	Antiseptic n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Clinical cure at 7 to 9 days				
Neher 2004	25/25	23/25		5.43[0.25,118.96]
Slack 1987	6/9	3/7		2.67[0.35,20.51]
van Balen 2003	19/65	31/73		0.56[0.28,1.14]
3.1.2 Clinical cure at 2 weeks				
Slack 1987	9/9	6/7		4.38[0.15,125.29]
van Balen 2003	37/65	60/73		0.29[0.13,0.62]

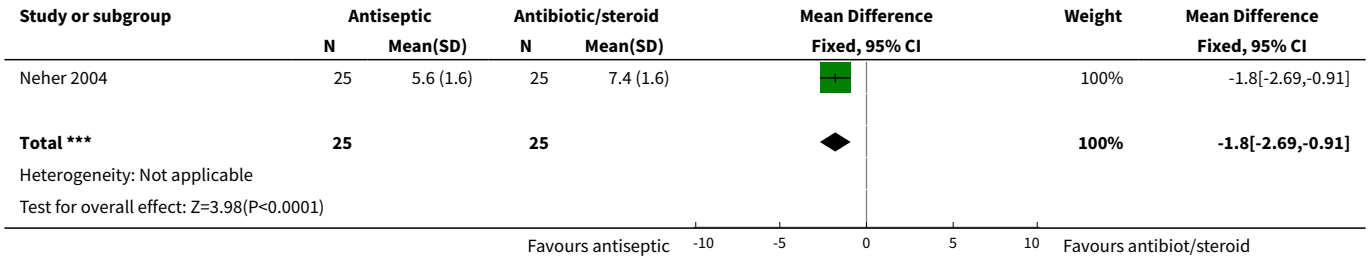




Analysis 3.2. Comparison 3 Topical: antibiotic/steroid vs antiseptic (Neher 2004: polymyxin B + neomycin + hydrocortisone vs N-chlorotaurine; Slack 1987: polymyxin B + neomycin + hydrocortisone vs boric acid; van Balen 2003: polymyxin B + neomycin + dexamethasone vs acetic acid), Outcome 2 Recurrence.



Analysis 3.3. Comparison 3 Topical: antibiotic/steroid vs antiseptic (Neher 2004: polymyxin B + neomycin + hydrocortisone vs N-chlorotaurine; Slack 1987: polymyxin B + neomycin + hydrocortisone vs boric acid; van Balen 2003: polymyxin B + neomycin + dexamethasone vs acetic acid), Outcome 3 Time to healing (days).



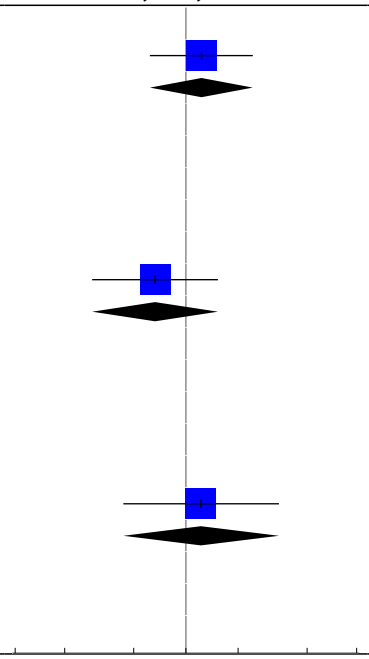
Comparison 4. Topical: antibiotic/steroid vs antiseptic/steroid (polymyxin B + neomycin + dexamethasone vs acetic acid + triamcinolone)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical cure at 1 week	1	134	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.62, 2.43]
1.2 Clinical cure at 2 weeks	1	134	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.29, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Clinical cure at 3 weeks	1	134	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.44, 3.44]
2 Recurrence between 3 and 6 weeks	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.60, 3.17]

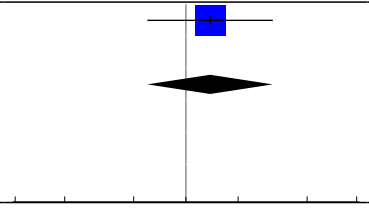
Analysis 4.1. Comparison 4 Topical: antibiotic/steroid vs antiseptic/steroid (polymyxin B + neomycin + dexamethasone vs acetic acid + triamcinolone), Outcome 1 Clinical cure.

Study or subgroup	Antiseptic/steroid n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Clinical cure at 1 week					
van Balen 2003	29/61	31/73		100%	1.23[0.62,2.43]
Subtotal (95% CI)	**61**	**73**		**100%**	**1.23[0.62,2.43]**
Total events: 29 (Antiseptic/steroid), 31 (Antibiotic/steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
4.1.2 Clinical cure at 2 weeks					
van Balen 2003	46/61	60/73		100%	0.66[0.29,1.53]
Subtotal (95% CI)	**61**	**73**		**100%**	**0.66[0.29,1.53]**
Total events: 46 (Antiseptic/steroid), 60 (Antibiotic/steroid)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$					
Test for overall effect: Z=0.96(P=0.34)					
4.1.3 Clinical cure at 3 weeks					
van Balen 2003	54/61	63/73		100%	1.22[0.44,3.44]
Subtotal (95% CI)	**61**	**73**		**100%**	**1.22[0.44,3.44]**
Total events: 54 (Antiseptic/steroid), 63 (Antibiotic/steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.7)					



Analysis 4.2. Comparison 4 Topical: antibiotic/steroid vs antiseptic/steroid (polymyxin B + neomycin + dexamethasone vs acetic acid + triamcinolone), Outcome 2 Recurrence between 3 and 6 weeks.

Study or subgroup	Antiseptic/steroid n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
van Balen 2003	15/57	14/68		100%	1.38[0.6,3.17]
Total (95% CI)	**57**	**68**		**100%**	**1.38[0.6,3.17]**
Total events: 15 (Antiseptic/steroid), 14 (Antibiotic/steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					

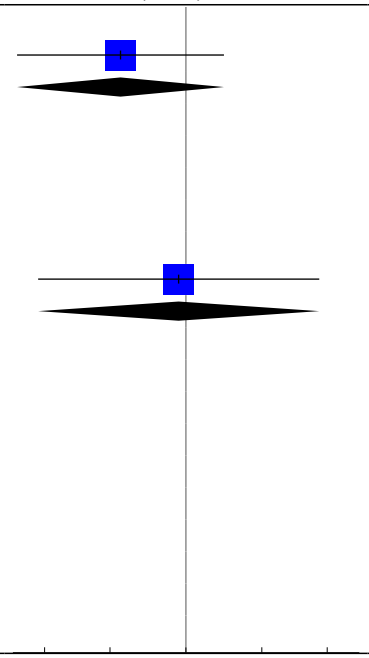


Comparison 5. Topical: antibiotic/steroid vs antibiotic/steroid/antifungal (polymyxin B + neomycin + hydrocortisone vs polymyxin B + flucinolone + econazole)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical cure at 7 to 9 days	1	15	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.24]
1.2 Clinical cure at 10 to 20 days	1	15	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.04, 16.85]
1.3 Clinical cure at 21 to 35 days	1	15	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Topical: antibiotic/steroid vs antibiotic/steroid/antifungal (polymyxin B + neomycin + hydrocortisone vs polymyxin B + flucinolone + econazole), Outcome 1 Clinical cure.

Study or subgroup	Antibiotic(AB)/steroid(S) n/N	AB/S/antifungal(AF) n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Clinical cure at 7 to 9 days					
Slack 1987	3/7	6/8		100%	0.25[0.03,2.24]
Subtotal (95% CI)	**7**	**8**		**100%**	**0.25[0.03,2.24]**
Total events: 3 (Antibiotic(AB)/steroid(S)), 6 (AB/S/antifungal(AF))					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.24(P=0.21)					
5.1.2 Clinical cure at 10 to 20 days					
Slack 1987	6/7	7/8		100%	0.86[0.04,16.85]
Subtotal (95% CI)	**7**	**8**		**100%**	**0.86[0.04,16.85]**
Total events: 6 (Antibiotic(AB)/steroid(S)), 7 (AB/S/antifungal(AF))					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.1(P=0.92)					
5.1.3 Clinical cure at 21 to 35 days					
Slack 1987	7/7	8/8			Not estimable
Subtotal (95% CI)	**7**	**8**			**Not estimable**
Total events: 7 (Antibiotic(AB)/steroid(S)), 8 (AB/S/antifungal(AF))					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

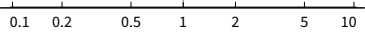


Comparison 6. Topical: antibiotic/steroid vs antibiotic/steroid (Roland 2004: ciprofloxacin+dexamethasone vs polymyxin B + neomycin + hydrocortisone; Wadsten 1985: framycetin + gramicidin + dexamethasone vs polymyxin B + oxytetracycline + hydrocortisone)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical cure	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Clinical cure at day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Clinical cure at day 8	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Clinical cure at day 18	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Microbial cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Microbial cure at day 10 to 20	1	349	Odds Ratio (M-H, Fixed, 95% CI)	2.94 [1.33, 6.50]

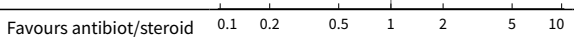
Analysis 6.1. Comparison 6 Topical: antibiotic/steroid vs antibiotic/steroid (Roland 2004: ciprofloxacin +dexamethasone vs polymyxin B + neomycin + hydrocortisone; Wadsten 1985: framycetin + gramicidin + dexamethasone vs polymyxin B + oxytetracycline + hydrocortisone), Outcome 1 Clinical cure.

Study or subgroup	Antibiotic/steroid n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Clinical cure at day 3				
Roland 2004	25/193	15/195		1.79[0.91,3.5]
6.1.2 Clinical cure at day 8				
Roland 2004	143/194	134/195		1.28[0.82,1.98]
6.1.3 Clinical cure at day 18				
Roland 2004	179/194	167/195		2[1.03,3.88]
Wadsten 1985	21/26	22/29		1.34[0.37,4.87]



Analysis 6.2. Comparison 6 Topical: antibiotic/steroid vs antibiotic/steroid (Roland 2004: ciprofloxacin +dexamethasone vs polymyxin B + neomycin + hydrocortisone; Wadsten 1985: framycetin + gramicidin + dexamethasone vs polymyxin B + oxytetracycline + hydrocortisone), Outcome 2 Microbial cure.

Study or subgroup	Antibiotic/steroid n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
6.2.1 Microbial cure at day 10 to 20					
Roland 2004	162/171	153/178		100%	2.94[1.33,6.5]
Subtotal (95% CI)	**171**	**178**		**100%**	**2.94[1.33,6.5]**
Total events: 162 (Antibiotic/steroid), 153 (Antibiotic/steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.67(P=0.01)					

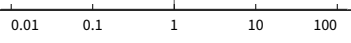


Comparison 7. Topical: antibiotic/steroid vs antibiotic (Schwartz 2006: polymyxin B + neomycin + hydrocortisone vs ofloxacin; Jones 1997: polymyxin B + neomycin + hydrocortisone vs ofloxacin; Mosges 2008: polymyxin B + neomycin + dexamethasone vs polymyxin B + neomycin)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Clinical cure at day 7 to 9	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Clinical cure at day 14 to 20	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Overall clinical-microbiological response in microbiologically evaluable patients	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Cured at day 7 to 9	1	90	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.44, 2.74]
2.2 Cured at day 14 to 20	2	284	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.31, 2.31]

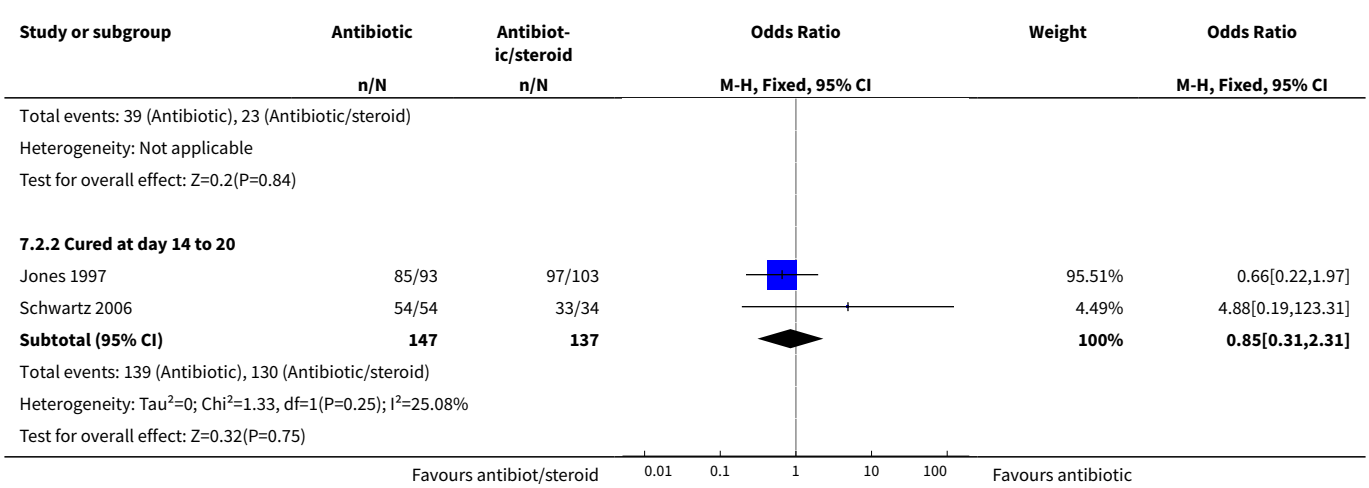
Analysis 7.1. Comparison 7 Topical: antibiotic/steroid vs antibiotic (Schwartz 2006: polymyxin B + neomycin + hydrocortisone vs ofloxacin; Jones 1997: polymyxin B + neomycin + hydrocortisone vs ofloxacin; Mosges 2008: polymyxin B + neomycin + dexamethasone vs polymyxin B + neomycin), Outcome 1 Clinical cure.

Study or subgroup	Antibiotic n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
7.1.1 Clinical cure at day 7 to 9				
Schwartz 2006	88/113	61/95		1.96[1.07,3.61]
7.1.2 Clinical cure at day 14 to 20				
Jones 1997	215/242	206/232		1.01[0.57,1.78]
Mosges 2008	64/164	84/164		0.61[0.39,0.94]
Schwartz 2006	109/113	91/95		1.2[0.29,4.92]



Analysis 7.2. Comparison 7 Topical: antibiotic/steroid vs antibiotic (Schwartz 2006: polymyxin B + neomycin + hydrocortisone vs ofloxacin; Jones 1997: polymyxin B + neomycin + hydrocortisone vs ofloxacin; Mosges 2008: polymyxin B + neomycin + dexamethasone vs polymyxin B + neomycin), Outcome 2 Overall clinical-microbiological response in microbiologically evaluable patients.

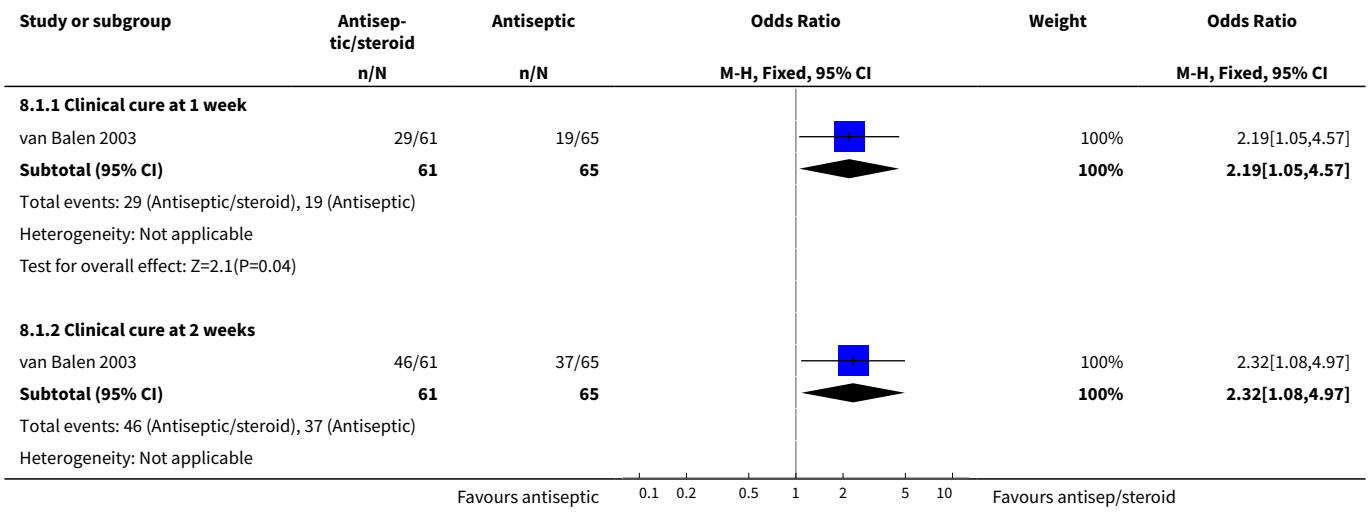
Study or subgroup	Antibiotic n/N	Antibiotic/steroid n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
7.2.1 Cured at day 7 to 9					
Schwartz 2006	39/56	23/34		100%	1.1[0.44,2.74]
Subtotal (95% CI)	**56**	**34**		**100%**	**1.1[0.44,2.74]**

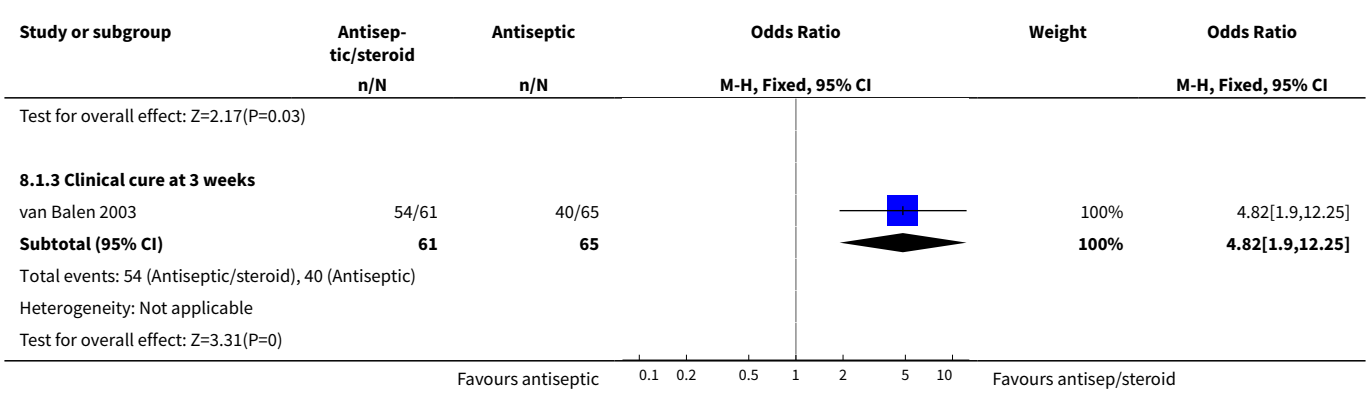


Comparison 8. Topical: antiseptic/steroid vs antiseptic (acetic acid + triamcinolone vs acetic acid)

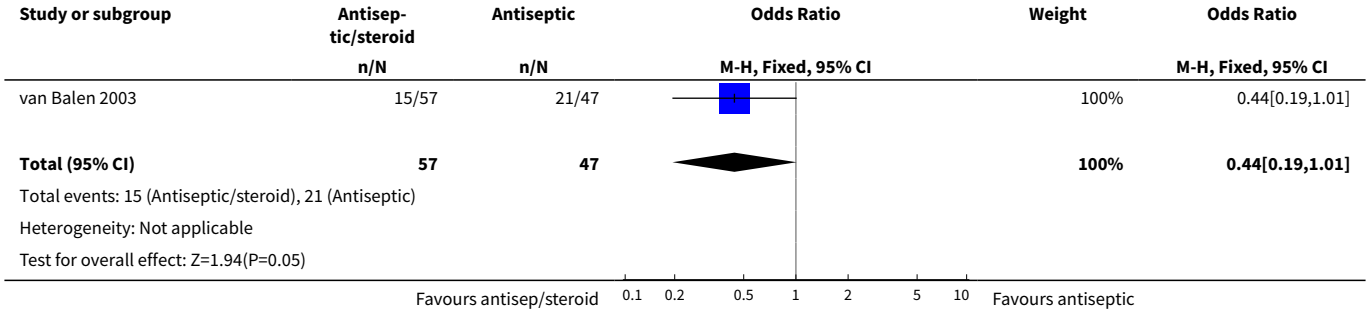
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical cure at 1 week	1	126	Odds Ratio (M-H, Fixed, 95% CI)	2.19 [1.05, 4.57]
1.2 Clinical cure at 2 weeks	1	126	Odds Ratio (M-H, Fixed, 95% CI)	2.32 [1.08, 4.97]
1.3 Clinical cure at 3 weeks	1	126	Odds Ratio (M-H, Fixed, 95% CI)	4.82 [1.90, 12.25]
2 Recurrence between 3 and 6 weeks	1	104	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.19, 1.01]

Analysis 8.1. Comparison 8 Topical: antiseptic/steroid vs antiseptic (acetic acid + triamcinolone vs acetic acid), Outcome 1 Clinical cure.





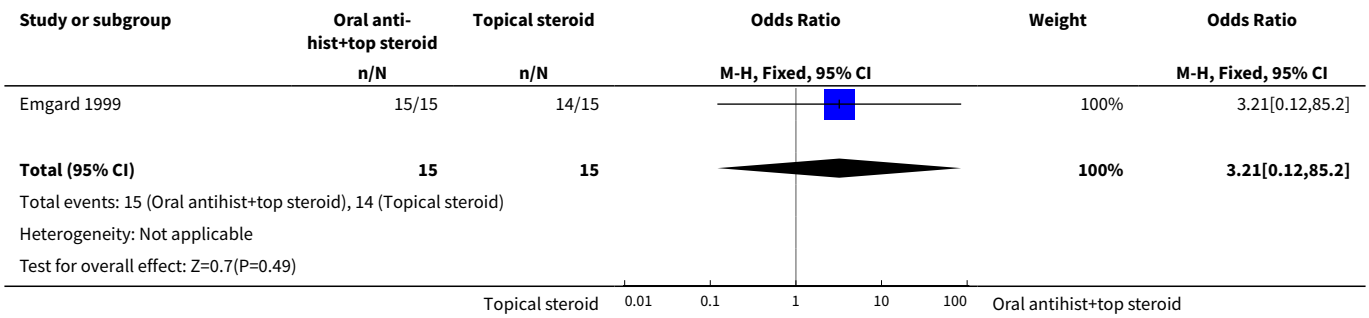
Analysis 8.2. Comparison 8 Topical: antiseptic/steroid vs antiseptic (acetic acid + triamcinolone vs acetic acid), Outcome 2 Recurrence between 3 and 6 weeks.



Comparison 9. Oral antihistamine + topical steroid vs topical steroid alone (oral loratadine + topical betamethasone vs topical betamethasone)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical cure at 3 weeks	1	30	Odds Ratio (M-H, Fixed, 95% CI)	3.21 [0.12, 85.20]

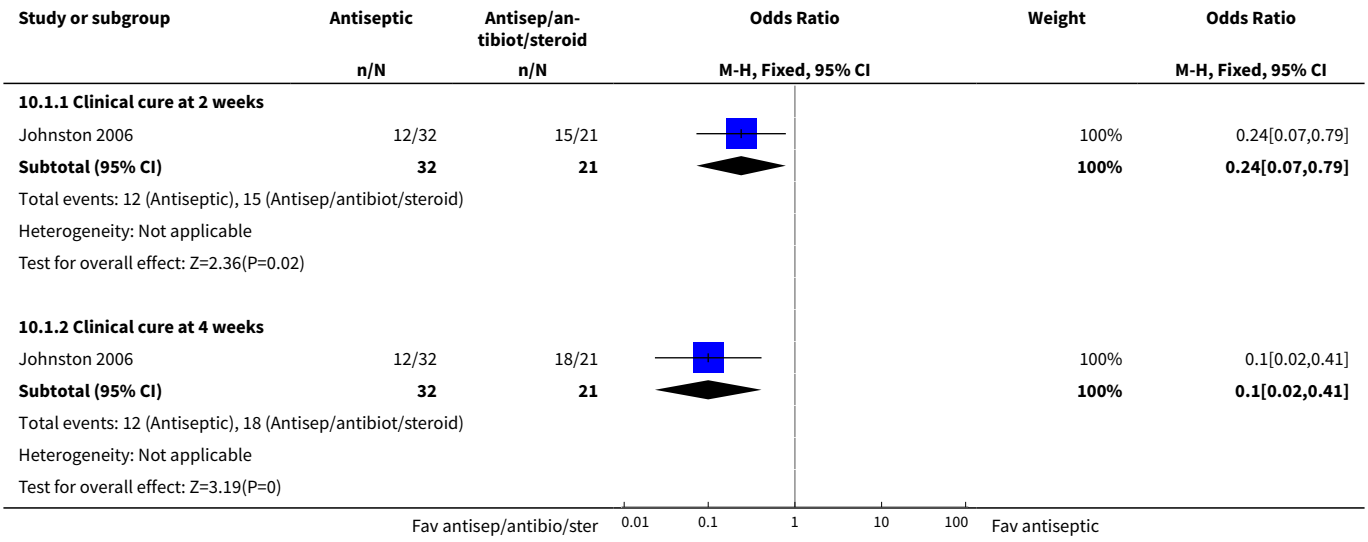
Analysis 9.1. Comparison 9 Oral antihistamine + topical steroid vs topical steroid alone (oral loratadine + topical betamethasone vs topical betamethasone), Outcome 1 Clinical cure at 3 weeks.



Comparison 10. Topical spray: antiseptic/antibiotic/steroid vs antiseptic (acetic acid + neomycin + dexamethasone vs acetic acid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical cure at 2 weeks	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.07, 0.79]
1.2 Clinical cure at 4 weeks	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.1 [0.02, 0.41]

Analysis 10.1. Comparison 10 Topical spray: antiseptic/antibiotic/steroid vs antiseptic (acetic acid + neomycin + dexamethasone vs acetic acid), Outcome 1 Clinical cure.



Comparison 11. Topical: glycerine vs aqueous vehicle (ciprofloxacin drops)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at 1 week	1	33	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 11.1. Comparison 11 Topical: glycerine vs aqueous vehicle (ciprofloxacin drops), Outcome 1 Clinical cure at 1 week.

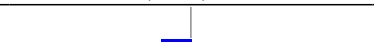
Study or subgroup	Glycerine n/N	Aqueous n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Olivera 2004	18/18	15/15			Not estimable
Total (95% CI)	**18**	**15**			**Not estimable**
Total events: 18 (Glycerine), 15 (Aqueous)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

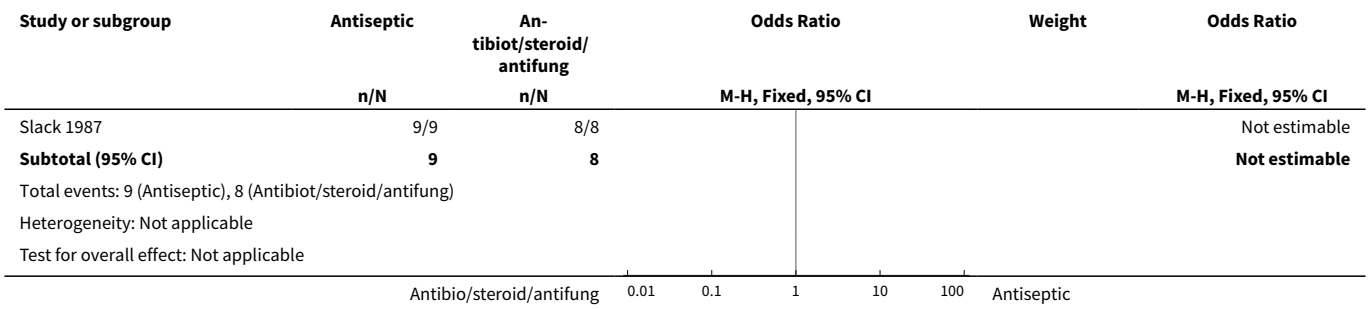
Comparison 12. Topical: antiseptic vs antibiotic/steroid/antifungal (boric acid vs polymyxin B + flucinolone + econazole)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Clinical cure at 1 week	1	17	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.08, 5.54]
1.2 Clinical cure at 2 weeks	1	17	Odds Ratio (M-H, Fixed, 95% CI)	3.8 [0.13, 107.31]
1.3 Clinical cure at 3 weeks	1	17	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 Topical: antiseptic vs antibiotic/steroid/antifungal (boric acid vs polymyxin B + flucinolone + econazole), Outcome 1 Clinical cure.

Study or subgroup	Antiseptic n/N	Antibiot/steroid/antifung n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
12.1.1 Clinical cure at 1 week					
Slack 1987	6/9	6/8		100%	0.67[0.08,5.54]
Subtotal (95% CI)	**9**	**8**		**100%**	**0.67[0.08,5.54]**
Total events: 6 (Antiseptic), 6 (Antibiot/steroid/antifung)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.71)					
12.1.2 Clinical cure at 2 weeks					
Slack 1987	9/9	7/8		100%	3.8[0.13,107.31]
Subtotal (95% CI)	**9**	**8**		**100%**	**3.8[0.13,107.31]**
Total events: 9 (Antiseptic), 7 (Antibiot/steroid/antifung)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.78(P=0.43)					
12.1.3 Clinical cure at 3 weeks					





ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study ID	Sequence generation	Allocation concealment	Balance at baseline	Blinding	Follow up	Quality of outcome assessment	Quality score
Cannon 1967	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Unclear Allocation concealment not reported	Yes, mostly Balanced across groups for age, sex, severity, duration of symptoms, bacteriology and precipitating factors Comorbidity not reported	Double-blind	Adequate No losses to follow up or exclusions were reported	Low	C
Emgard 1999	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Unclear Allocation concealment not reported	Yes, mostly Comparable across treatment groups for age, sex, and severity Precipitating factors and comorbidity not reported	Double-blind	Adequate No loss to follow up or exclusions reported	High	C
Freedman 1978	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Adequate Both solutions were packaged in coded, identical appearing 10 ml bottles	Yes, partially Balanced for age, sex, severity and bacteriology Comorbidity and precipitating factors not reported	Double-blind	Inadequate 30.8% (28/91) drop-out	Satisfactory	C
Johnston 2006	Unclear	Adequate	Nil mentioned	Single-blind (evaluator)	Adequate	Low (not described in detail)	C

Table 1. Methodological quality of included studies *(Continued)*

	Treatment allocation described as random, but method of sequence code generation was not stated	Randomisation was conducted by the clinical trials department, using a series of numbered envelopes, blind to the clinician			6.4% (7/109) had missing outcome data		
Jones 1997	Adequate Participants were randomly assigned according to a computer-generated randomised schedule	Adequate The drug was dispensed by a coordinator not involved in the subject evaluation	Yes Balanced for age, sex, race, laterality, duration of otitis externa, sign and symptom score, severity and bacteriology Precipitating factors and comorbidity not reported Cortisporin®-treated children were more likely than ofloxacin ones to be excluded from the clinically evaluable population because of missed visits	Single-blind (evaluator)	Inadequate 21.1% (127/601) drop-out	High	C
Masood 2008	Adequate A computer random number generator was used	Not used The medicated dressings differ in colour and smell	Yes Comparable across groups for age, sex, comorbidity, precipitating factors and bacteriology	Single-blind	Adequate No loss to follow up at 48 hours	High	B

Table 1. Methodological quality of included studies *(Continued)*

			Balanced for pain scores at baseline but no baseline data across groups for clinical signs				
Mosges 2007	Adequate Randomisation list created in blocks of 4 using Rancode +	Unclear Allocation concealment not reported	Yes Comparable across groups for age, sex, severity, bacteriology, former episodes of otitis externa and duration of current episode Comorbidity and precipitating factors not reported	Double-blind	Borderline 12.1% (18/149) drop-out	Satisfactory	B
Mosges 2008	Adequate Computer generated in blocks of 4	Adequate The medication was filled in identical plastic bottles and the labelling was masked by using the study code and the randomisation number	Yes, mostly Balanced for age, sex, ethnicity, weight Precipitating factors, comorbidity, severity and bacteriology not reported	Double-blind	Adequate 8% (27/337) discontinued	High	A
Neher 2004	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Unclear Allocation concealment not reported	Yes, mostly Balanced for age, sex, severity, and bacteriology Precipitating factors and co-	Double-blind	Adequate No loss to follow up or exclusions reported	Satisfactory	C

Table 1. Methodological quality of included studies *(Continued)*

			morbidity not reported				
Olivera 2004	Adequate Randomly generated numbers were used	Adequate The treatments were labelled with randomly generated numbers	Yes, mostly Balanced for age, severity and bacteriology More males in the ciprofloxacin glycerin versus aqueous group (14:4 versus 4:11) Comorbidity and precipitating factors not reported	Double-blind	Borderline 10.8% (4/37) drop-out	Satisfactory	A
Roland 2004	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Unclear Allocation concealment not reported	Yes, partially Balanced for age, sex, and severity Ciprofloxacin/dexamethasone group has significantly less gram negative and significantly more gram positive bacterial isolates Precipitating factors and comorbidity not reported	Single-blind (evaluator)	Adequate 1.8% (7/396) drop-out	Satisfactory	C
Roland 2007	Unclear	Adequate	Yes, mostly	Single-blind (evaluator)	Unclear (524 assessed; unclear as to how	Low quality (VAS would	C

Table 1. Methodological quality of included studies *(Continued)*

	Treatment allocation described as random, but method of sequence code generation was not stated	Only the designated individual assigned to dispense the test article had access to the specific dosing regimen and provided instructions to patients	Balanced for age, sex, duration of symptoms, number of previous episodes of acute otitis externa and severity Precipitating factors and co-morbidity not reported		many were randomised)	have been better)	
Roland 2008	Unclear Treatment allocation described as random, but method of sequence code generation was not stated (prepared by Alcon Research Ltd Biostatistics Dept)	Adequate Strict avoidance of discussions among staff members that might reveal treatment assignments was mandated by the protocol	Yes, partially Matched for age, sex and bacteriology Precipitating factors and co-morbidity not reported	Single-blind (evaluator)	Adequate 3.3% (5/151) drop-out	Satisfactory	B
Sabater 1996	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Adequate Patients received a coded container labelled as sample A or sample B	No There were more severe cases present in the ciprofloxacin group (according to the discussion text) Nil reported for age, sex, precipitating factors and co-morbidity etc.	Double-blind	Adequate No loss to follow up or exclusions reported	Low	C
Schwartz 2006	Adequate Used a computer-generated scheme	Adequate Used an interactive voice randomisation system	Yes Balanced for age, sex, dura-	Single (evaluator)-blind	Inadequate 21.5% (60/278) drop-out	High	C

Table 1. Methodological quality of included studies *(Continued)*

			tion, severity and bacteriology Precipitating factors and co-morbidity not reported, but may not be so important as this was a paediatric population		However this study is to be commended for its detailed attrition data unlike others		
Slack 1987	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Unclear Allocation concealment not reported	No The boric acid group (group A) had higher severity scores but none in this group cultured pseudomonas	Double-blind	Borderline 14.3% (4/28) drop-out	Satisfactory	C
Tsikoudas 2002	Adequate Used a computer-generated scheme	Adequate Patients were sent to the pharmacy department to be randomised	Yes, only for severity	Double-blind	Inadequate 33% (13/39) drop-out	High 10 cm linear analogue assessment sheet	C
van Balen 2003	Adequate Used a computer-generated scheme	Adequate Hospital pharmacy supplied general practitioners with identical brown bottles containing the ear drops	Yes Comparable across groups for age, sex, severity, co-morbidity and precipitating factors Bacteriology not investigated	Double-blind	Borderline 10.8% (190/213) drop-out	High	A

Table 1. Methodological quality of included studies *(Continued)*

Wadsten 1985	Unclear Treatment allocation described as random, but method of sequence code generation was not stated	Unclear Allocation concealment not reported	Not reported	Single-blind (evaluator)	Borderline 14% (9/64) drop-out	Low	C

Table 2. Bilateral disease: numbers for ears versus participants

Study ID	# Participants	# Ears	% Bilateral cases	Handling bilateral cases	Results: patient or ears
Cannon 1967	Number randomised: not reported 40 analysed: 20 Neo-Medrol; 20 placebo	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Emgard 1999	30 randomised and analysed: 15 betamethasone plus loratadine; 15 betamethasone plus placebo	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Freedman 1978	91 randomised: 47 Coly-Mycin S®; 44 placebo Analysed: 91 at day 1, 87 at day 3, 79 at day 7, 28 at day 21	Not reported	Not reported although some patients did have bilateral infections	"In patients with bilateral infections, response to therapy was statistically analysed for only one ear, which was chosen randomly"	Participants
Johnston 2006	109 randomised and analysed By diagnosis and treatment: 53 acute otitis externa (32 EarCalm®; 21 Otomize®); 56 infected mastoid cavities (29 EarCalm®; 27 Otomize®)	109 randomised and analysed	Zero	Not applicable	Participants
Jones 1997	601 randomised: 314 adults (158 ofloxacin, 156 Cortisporin®); 287 children (143 ofloxacin, 144 Cortisporin®) 474 clinically evaluable/analysed: 247 adults (126 ofloxacin, 121 Cortisporin®); 227 children (116 ofloxacin, 111 Cortisporin®)	Number randomised ears: not reported 552 ears clinically evaluable: (280 ofloxacin, 272 Cortisporin®)	Analysed participants: 76 (38 ofloxacin, 38 Cortisporin®)	Unclear, but results reported at participant level	Participants
Masood 2008	64 randomised participants 64 analysed (32 Triadcortyl, 32 glycerine-ichthammol)	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Mosges 2007	152 randomised participants 149 analysed by intention-to-treat (77 antibiotic with steroid, 72 antibiotic only)	152 randomised ears	Zero	Not applicable	Participants

Table 2. Bilateral disease: numbers for ears versus participants *(Continued)*

	131 analysed on per-protocol basis (70 antibiotic with steroid, 61 antibiotic only)				
Mosges 2008	338 randomised participants 328 analysed (164 antibiotic, 164 antibiotic/steroid)	338 randomised ears 328 analysed ears	Zero	Not applicable	Participants
Neher 2004	50 randomised and analysed: 25 NCT; 25 Otosporin®	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Olivera 2004	37 randomised participants; not available by treatment group 33 analysed: 15 ciprofloxacin aqueous; 18 ciprofloxacin glycerin	37 randomised ears 33 ears analysed	Zero	Not applicable	Participants
Roland 2004	468 randomised participants: 232 Cip/Dex; 236 NPH Participants analysed: 396 modified intention-to-treat analysed: (197 Cip/Dex; 199 NPH), day 3: 388, day 8: 389, day 18: 389	511 randomised ears (259 Cip/Dex; 252 NPH) 432 ears analysed (221 Cip/Dex; 211 NPH)	Randomised participants: total: 43/468 (9.2%), Cip/Dex 27/232 (11.6%), NPH 16/236 (6.8%) Analysed participants: modified intention-to-treat: 36/396 (9.1%), Cip/Dex 24/197 (12.2%), NPH 12/199 (6.0%)	Unclear, but results reported at participant level	Participants
Roland 2007	524 analysed. No further data provided.	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Roland 2008	206 randomised participants (106 Cipro/hydrocortisone; 100 neomycin/polymyxin B/hydrocortisone + amoxicillin) 151 analysed per protocol (82 Cipro/HC; 69 NPH + amoxicillin) 129 analysed modified per protocol (70 Cipro/HC; 59 NPH + amoxicillin)	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Sabater 1996	Number randomised participants: not reported Number analysed: by diagnosis and treatment: 54 diffuse otitis externa (30 ciprofloxacin; 24 gentamicin); 47 simple chronic otitis media (20 ciprofloxacin; 27 gentamicin)	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants

Table 2. Bilateral disease: numbers for ears versus participants *(Continued)*

Schwartz 2006	278 paediatric participants randomised: 140 ofloxacin; 138 NPHc Participants analysed: 268 intention-to-treat: 135 ofloxacin; 133 NPHc 208 clinically evaluable: 113 ofloxacin; 95 NPHc	Randomised ears: not reported Analysed ears: 237 clinically evaluable ears (131 ofloxacin;106 NPHc)	Randomised rate: not reported Analysed rate: clinically evaluable population 29/208 (13.9%)	In bilateral disease, the ear with the highest overall score was designated the 'target ear'. The right ear was the designated 'target ear' in the case of identical scores obtained in bilateral disease	Participants
Slack 1987	28 randomised: not available by treatment group 24 analysed: 9 boric acid; 7 NPH; 8 polymyxin B/fluocinolone/econazole	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participants
Tsikoudas 2002	39 randomised: 17 Vista-Methasone®; 22 Vista-Methasone N®) 35 analysed:15 Vista-Methasone®; 20 Vista-Methasone N®	Not reported	Not mentioned explicitly but likely to be zero as results were reported at participant level	Not applicable	Participant
van Balen 2003	213 randomised: 71 acetic acid; 63 steroid/acetic acid; 79 steroid/antibiotic Analysed participants: 202 at day 7, 198 at day 14, 190 at day 21	Randomised ears: total 282 ears (89 acetic acid; 88 steroid/acetic acid; 105 steroid/antibiotic) Analysed ears: not reported	Randomised rate: 69/213 (32.4%) Analysed rate: not reported	Unclear, but results reported at participant level	Participants
Wadsten 1985	64 randomised; not available by treatment group 55 analysed: 26 Sofradex®; 29 TPB	Not reported	Not mentioned explicitly but likely to be zero as results were reported by participant	Not applicable	Participants

Cip = ciprofloxacin
Cip/Dex = ciprofloxacin + dexamethasone
Cip/Hc = ciprofloxacin + hydrocortisone
CSOM = chronic suppurative otitis media
NCT = N-chlorotaurine
NPH = neomycin + polymyxin B + hydrocortisone
NPHc = polymyxin B + neomycin sulphate + hydrocortisone
PNHc = polymyxin B + neomycin + hydrocortisone
TP = trimethoprim + polymyxin B
TPB = oxytetracycline + hydrocortisone with polymyxin B
TSP = trimethoprim + polymyxin B + sulfacetamide

Table 3. Participant eligibility criteria, including acute otitis externa diagnostic criteria

Study ID	Definition of acute otitis externa	Inclusion criteria	Exclusion criteria	Are the acute otitis externa results reported separately?	Randomisation by stratification performed?	PPA or ITT analysis?
Cannon 1967	Not stated	Otitis externa	Not stated	Not applicable	Not applicable	PPA
Emgard 1999	Not stated	Patients with otitis externa	Patients receiving oral corticosteroids within 30 days of the start of the study. Patients with known neoplasm, diabetes mellitus, multiple drug hypersensitivity, lactose intolerance, pregnant or breast-feeding women, those planning to become pregnant.	Not applicable	Not applicable	PPA; ITT by default as no losses
Freedman 1978	Not stated	Patients with acute otitis externa	Not stated	Not applicable	Not applicable	PPA
Johnston 2006	Acute onset of generalised inflammation of external auditory canal skin	Adults with acute otitis externa or infected mastoid cavities	Presence of cholesteatoma, aural polyps or congenital abnormalities; significant canal stenosis or false fundus either requiring a wick or systemic antibiotics; chronic otitis externa or acute exacerbation of chronic otitis externa and necrotising otitis externa. Other groups excluded were those with concomitant systemic disease, immunocompromised, under the age of 16, pregnant or contraindicated within formulary guidelines	Yes	Yes	ITT (allocating an 'explicit allocation of poor outcome' (i.e. no cure) to those that did not complete the protocol
Jones 1997	Clinically diagnosed otitis externa with purulent or mucopurulent otorrhoea	Unilateral or bilateral stable or exacerbating otitis externa of 2 weeks or less duration with purulent or mucopurulent otorrhoea, males, premenarchal females, women not of childbearing potential, women of childbearing potential with a negative urine pregnancy test and reliable contraception being practiced	20 criteria listed including, perforated ear drums within the previous 6 weeks, chronic otitis externa, seborrhoeic dermatitis of the pinna or ear canal, recent systemic/topical antibiotics, allergy/sensitivity to any test medication	Not applicable	Not applicable	PPA; some ITT analysis also performed
Masood 2008	Clinically diagnosed severe acute otitis ex-	Adults (> or = 18 years old) with severe acute otitis externa for less than 3 weeks	Recurrent chronic otitis externa, co-existing middle-ear pathology, those requiring topical/systemic antibiotics within the	Not applicable	Not applicable	ITT

Table 3. Participant eligibility criteria, including acute otitis externa diagnostic criteria *(Continued)*

	terna characterised by otalgia, otorrhoea, itching, hearing loss and oedematous ear canal		past 3 weeks, possible or known drug sensitivity to agents used			
Mosges 2007	Not stated	Acute otitis externa	Known viral, fungal or tuberculous ear infections, otitis media, mastoiditis, mastoid cavities, stenosis, exostosis, cholesteatoma, perforated tympanum, invasive malignant otitis externa, pretreatment of the current otitis externa with antibiotics or corticosteroids, diabetes, use of immunosuppressants, the need for systemic antibiotic or corticoid treatment, or the possible use of analgesics other than paracetamol during the study	Not applicable	Not applicable	Both ITT and PPA were used (no relevant differences were found)
Mosges 2008	Not stated explicitly	Adults with a diagnosis of acute unilateral bacterial otitis externa and a previous episode of otitis externa within the last 2 months	Otitis externa from viral, fungal or tubercular agents, otitis media, mastoiditis, mastoid cavities, stenosis, exostosis, cholesteatoma, perforated tympanic membrane, invasive malignant chronic otitis externa, (pre-) treatment with local/systemic antibiotics or corticoids, use of analgesics or NSAIDs other than paracetamol, diabetes mellitus, application of immunosuppressants, vaccination reactions, intolerance/hypersensitivity to one of the study drugs or paracetamol, severe hepatic or renal insufficiencies, alcohol abuse, existing or intended pregnancy, lactation, well-founded doubt about the patients co-operation, participation in another clinical trial or previous participation in this trial.	Not applicable	Not applicable	PPA, although they did talk about ITT populations
Neher 2004	Not stated	Patients with acute otitis externa (diagnosed by an ENT doctor at the outpatient department)	Malignant otitis externa, topical treatment with other agents, systemic application of antibiotics or corticoids, pregnancy, and participation in another study at the same time	Not applicable	Not applicable	ITT by default: (no losses to follow up and no exclusions)

Table 3. Participant eligibility criteria, including acute otitis externa diagnostic criteria *(Continued)*

Olivera 2004	Drainage, swelling, pain, and/or erythema in the external ear canal and bacteriologic confirmation of infection	Acute otitis externa manifested as drainage, swelling, pain, and/or erythema in the external ear canal. Bacteriologic confirmation of infection. An ability to follow investigator's instructions.	Allergy or contraindication to quinolones. The need to start an incompatible treatment during the study period. Chronic illness requiring long-term pharmacologic therapy. Participation in another clinical trial during the previous 15 days.	Not applicable	Not applicable	PPA
Roland 2004	A diffuse cellulitis and bacterial infection of the external auditory meatus that may involve underlying structures	Patients 1 year and over with a clinical diagnosis of mild, moderate or severe acute otitis externa of less than 4 weeks duration in 1 or both ears and intact ear drums	Acute or chronic otitis media, post-tympanostomy tube acute otorrhoea, malignant otitis externa, overt fungal or viral ear infections, congenital abnormalities of the ear canal, obstructive bony exostoses, mastoid or other suppurative non-infectious ear disorders, seborrhoeic dermatitis of the ear canal, a current or prior history of immunosuppressive disorders, acute or chronic renal insufficiency, hepatitis, diabetes mellitus, pregnancy, lactation	Not applicable	Not applicable	PPA; although they also talk about ITT and modified ITT populations
Roland 2007	A diffuse cellulitis and bacterial infection of the skin and subdermis of the ear canal	Patients 1 year and over with a clinical diagnosis of moderate (constant but tolerable pain) or severe (intense and unrelenting pain) acute otitis externa of less than 4 weeks duration in 1 or both ears and intact tympanic membranes	Clinically diagnosed chronic suppurative otitis media, acute otitis media, acute otorrhoea, clinically diagnosed malignant otitis externa, overt fungal or viral infection, congenital abnormalities of the external auditory canal, mastoiditis or other suppurative non-infectious ear disorders, malignant tumour of the external auditory canal, prior history of otologic surgery (except surgery confined to the temporomandibular joint), immunosuppressive disorders, current or prior use of systemic (within 30 days) or topical (7 days) steroids, infection requiring systemic antibiotics, current use of topical or oral antibiotics or analgesics (except acetaminophen) or treatment with alcohol, vinegar, or other astringents, known sensitivity to any study medication, or pregnancy or lactation	Not applicable	Not applicable	PPA
Roland 2008	Clinical diagnosis of acute otitis externa	1 year of age and over, had a diagnosis of mild, moderate or severe acute otitis externa, severity of symptoms at least "mild". Acute otitis	Acute otitis externa symptoms present for 2 days or less; non-intact tympanic membrane, with or without otorrhoea. Acute otitis media, malignant	Not applicable	Not applicable	PPA

Table 3. Participant eligibility criteria, including acute otitis externa diagnostic criteria *(Continued)*

		externa symptoms present for longer than 2 days. Patients to refrain from water immersion of the ear during the study. Informed consent given. Agreement to comply with protocol requirements.	otitis externa, chronic suppurative otitis media, mastoiditis, seborrheic dermatitis of the external auditory canal, or other suppurative non-infectious ear disorders. Known or suspected fungal, viral or mycobacterium ear infections. Diabetes, immunosuppressive disorders, renal abuse, hepatitis, mononucleosis, chronic diarrhoea, narcotic abuse. Concomitant use of ear washes, systemic antibiotic agents, steroids, analgesics other than acetaminophen, and any preparation that might obscure study results. Known or suspected allergy to any component of study medications			
Sabater 1996	A bacterial infection that progresses as an acute dermatitis of the external auditory meatus where the most frequent causal pathogen is *Pseudomonas aeruginosa*	Patients with acute diffuse otitis externa and simple chronic suppurative otitis media	Patients under 18 years of age, pregnant or lactating women, allergies to the drugs used in the study, severe renal or liver failure, patients treated with antibiotics within 7 days of entering the study, or patients with chronic suppurative otitis media who had hearing loss greater than 60 dB	Yes	Yes	PPA
Schwartz 2006	An infection of the external auditory canal associated with symptoms of local pain and tenderness	Paediatric patients greater than or equal to 6 months and less than or equal to 12 years of age with stable or exacerbating symptoms of otitis externa of less than 2 weeks duration with otitis externa of presumed bacterial origin. The presence in one or both ears of scores greater than or equal to 2 for oedema and tenderness, a score of greater than or equal to 1 or erythema (0 = none, 1 = mild, 2 = moderate, 3 = severe) and a score greater than or equal to 1 for ear secretion/exudates (0 = none, 1 = serous, 2 = mucopurulent, 3 = purulent). The sum of all scores required for enrolment was greater than or equal to 6.	The presence of a perforated tympanic membrane in the preceding 6 months; chronic otitis externa (current episode greater than or equal to 2 weeks); seborrhoeic dermatitis in the external ear canal or pinna; invasive otitis externa requiring systemic antibiotics; therapy in the preceding 7 days with systemic or topical antibiotics, steroids, or non-steroidal anti-inflammatory drugs; over-the-counter therapy in the preceding 36 hours; known or suspected allergy to quinolones or any ingredients of the test medications; and infection suspected to be resistant to the study drugs	Not applicable	Not applicable	PPA and ITT

Table 3. Participant eligibility criteria, including acute otitis externa diagnostic criteria *(Continued)*

Slack 1987	Not stated	Patients with otitis externa in whom no treatment had been given for at least 2 weeks	Previous mastoid surgery and visible perforated ear drum	Not applicable	Not applicable	PPA
Tsikoudas 2002	An oedematous ear canal with moist keratin debris within it	Adults with otitis externa	Age less than 18 years, neomycin allergy, ear canal oedema severe enough to prevent the use of topical ear drops, concurrent middle ear disease, patients requesting exclusion	Not applicable	Not applicable	PPA
van Balen 2003	Redness or swelling of the external auditory canal or debris within the canal, accompanied by pain, itchiness, otorrhoea, hearing loss or a stuffy feeling for less than 3 weeks	Patients with signs and symptoms of acute otitis externa	Age 17 years or younger, pregnancy, chronic otitis externa (more than 3 weeks), a furuncle in the external auditory canal, acute otitis media, a perforated ear drum, perichondritis, fever, allergy to any of the study drops, having already been recruited to the study or been treated for acute otitis externa in the past month	Not applicable	Not applicable	PPA
Wadsten 1985	Not stated	Patients with acute otitis externa	Recent treatment for external otitis, fever, perichondritis or perforated ear drums	Not applicable	Not applicable	PPA

ITT = intention-to-treat
PPA = per-protocol analysis

Table 4. Intervention regimens used

Study ID	Intervention - category (all are topical unless otherwise stated)	Intervention - specific	Duration	Ear cleaning	Concurrent medication
Cannon 1967	Antibiotic/steroid versus placebo (its vehicle)	Methylprednisolone disodium phosphate (1.33 mg/ml) and neomycin sulphate (5 mg/ml) + 'vehicle' versus the 'vehicle'. The 'vehicle' comprised sodium citrate, sodium chloride, polysorbate 80, sodium bisulphite, phenethyl alcohol, benzalkonium chloride and sodium hydroxide.	10 days	All groups: performed on initial visit and again, if necessary, at day 5 and day 10 follow-up examinations	Concurrent medication: not reported

Table 4. Intervention regimens used *(Continued)*

		Dose: 4 drops 3 times daily			
Emgard 1999	Steroid versus steroid + oral antihistamine	0.5% betamethasone dipropionate (Diprosone®) + loratadine 20 mg od 10/7 versus 0.5% betamethasone dipropionate + oral placebo (no further details provided about this) Dose: ear drops; 4 drops 4 times daily for the first week, 4 drops once daily from day 8 to 11	11 days	Unclear; suction appears to have been used selectively for those with otorrhoea	Concurrent medication: no oral corticosteroids within the preceding 30 days; no antibiotics or anti-inflammatory drugs allowed during the study; paracetamol permitted for pain
Freedman 1978	Antibiotic/steroid versus placebo	Coly-Mycin S® (each ml contains colistin sulphate 3 mg + neomycin sulphate 3.3 mg + hydrocortisone acetate 10 mg (1%); thonzonium bromide 0.5 mg (0.05%), polysorbate '80', acetic acid and sodium acetate in a buffered vehicle; thimerosal 0.002% added as a preservative) versus placebo (a starch solution with a turbidity matching that of the antibiotic drop) Dose: 4 drops 3 times daily	21 days	All groups: performed at initial visit and days 3 and 7. A wick was inserted for the first 2 days.	Concurrent medication: at least 8 patients had other antibiotics or steroids (1 in active group; 7 in placebo group)
Johnston 2006	Acidifying agent versus acidifying agent/antibiotic/steroid	2% glacial acetic acid (EarCalm®) versus 2% glacial acetic acid, 0.1% dexamethasone and 3250 U/ml neomycin sulphate (Otomize®) Dose: 1 puff 3 times a day	2 weeks initially; if not cured at this stage a further 2 weeks of therapy was given	All groups: performed on entry to the study; those with active disease at 2 week follow up underwent further aural toilet prior to continuing with the same therapy for a further 2 weeks	Concurrent medication: excluded those requiring systemic antibiotics
Jones 1997	Antibiotic (Q) versus antibiotic/steroid	Ofloxacin 0.3% 10 drops twice daily adults, 5 drops twice daily children versus Cortisporin® (neomycin + polymyxin B + hydrocortisone) 4 drops 4 times daily adults, 3 drops 4 times daily children Dose: see above	10 days	Not specified	Concurrent medication: no systemic antimicrobials; no systemic or topical antimicrobials in preceding 14 days; no systemic or topical quinolones in preceding 30 days; no non-prescription therapy for otitis externa in preceding 36 hours; excluded long-term users of analgesics and/or anti-inflammatory drugs. Allowance of topical antimicrobials for acne or analgesic and anti-inflammatory therapy if the dose had been stable for at least 14 days or 1 month respectively

Table 4. Intervention regimens used *(Continued)*

Masood 2008	Antibiotic/steroid/anti-fungal dressing versus antiseptic/astringent dressing	10% glycerine-ichthammol (GI) solution on ribbon gauze versus Triadcortyl® ointment on ribbon gauze (triamcinolone acetonide 0.1%, gramicidin 0.025%, neomycin sulphate 0.25%, nystatin 100,000 units/g)	48 hours	All groups: performed at initial visit	Nil mentioned
Mosges 2007	Antibiotic/steroid versus antibiotic	Polymyxin B sulfate (7500 IE/g) + bacitracin (300 IE/g) + hydrocortisone acetate (10 mg/g) ointment (Polyspectran® HC Salbe) versus polymyxin B sulfate (7500 IE/g) + bacitracin (300 IE/g) ointment Dose: medicated gauze strip inserted on day 0 and removed by patient after 24 hours. Then ointment applied twice daily. Then medicated gauze strip inserted on day 3 to 5 and removed 24 hours later by the patient. Then ointment applied twice daily.	10 days	Not mentioned	Only paracetamol was permitted
Mosges 2008	Antibiotic versus antibiotic/steroid	Polymyxin B sulfate 7500 IU + neomycin sulfate 3500 IU versus dexamethasone sodium phosphate 0.132% + polymyxin B sulfate 7500 IU + neomycin sulfate 3500 IU Dose: 2 drops 3 times daily	10 days	Not mentioned	Only paracetamol was permitted
Neher 2004	Antiseptic (endogenous) versus antibiotic/steroid	2 ml 1% NCT (N-chlorotaurine) once daily versus 1 ml Otosporin® (1.27 mg polymyxin B sulphate + 5 mg neomycin sulphate + 10 mg hydrocortisone per ml) once daily Dose: see above	Until cure (9 days in vast majority of cases)	Not specified. The substances were applied to the outer ear canal using a rolled cotton wick soaked with the agent. This ear wick was left in place and was changed daily.	Concurrent medication: excluded those on topical treatment with other agents, those on systemic antibiotics or corticoids
Olivera 2004	Glycerin antibiotic (Q) versus aqueous antibiotic (Q)	0.3% ciprofloxacin glycerin solution versus 0.3% ciprofloxacin aqueous solution Dose: 3 drops twice daily	7 days	Not performed	Concurrent medication: excluded patients that needed to start an incompatible treatment during the study period, and those requiring long-term pharmacotherapy for a chronic illness
Roland 2004	Antibiotic/steroid (Q) versus antibiot-	Ciprodex® (0.3% ciprofloxacin + 0.1% dexamethasone) (3 drops twice daily for children, 4 drops twice daily for 12 years and over) versus Cortisporin® (neomycin 0.35% + polymyxin B 10,000	7 days	Performed at initial visit and at follow-up visits if needed	Concurrent medication: washout period required prior to commencing the study; 3 days for short-acting antibiotics or 7 days for long-acting antibi-

Table 4. Intervention regimens used *(Continued)*

	ic/steroid (NQ)	IU/ml + hydrocortisone 1.0%) (3 drops 3 times daily for children, 4 drops 3 times daily for 12 years and over) Dose: see above			otics. Systemic or otic corticosteroids, topical treatment with alcohol, vinegar or other astringent medication, systemic antimicrobial therapy, non-steroidal or other inflammatory drugs was not permitted. Analgesic use was restricted to acetaminophen with or without codeine.
Roland 2007	Antibiotic/steroid (Q) versus antibiotic/steroid (NQ)	Ciprofloxacin 0.3% + dexamethasone 0.1% (3 drops twice daily (adults); 4 drops twice daily (children)) versus neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1.0% (3 drops 3 times daily (adults); 4 drops 3 times daily (children)) Dose: see above	7 days	Nil mentioned	Acetaminophen and codeine use permitted
Roland 2008	Antibiotic/steroid (Q) drop with an (NQ) antibiotic/steroid drop plus oral antibiotic	Ciprofloxacin 0.2% + hydrocortisone 1% (3 drops twice times daily x 7 days) versus neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1% (adults: 4 drops 3 times daily + up to 500 mg amoxicillin 3 times daily for 10 days; children: 3 drops 3 times daily + 40 mg/kg/day in 3 divided doses for 10 days) Dose: see above	7 or 10 days depending on treatment group	At entry infected ears cleansed of fluid and debris using lavage, dry mop or suction	Use of acetaminophen permitted
Sabater 1996	Antibiotic (Q) versus antibiotic (NQ)	0.5% ciprofloxacin versus 0.3% gentamicin Dose: 5 drops 3 times daily	8 days	Not performed	Concurrent medication: no antibiotics in the preceding 7 days
Schwartz 2006	Antibiotic (Q od) versus antibiotic/steroid (NQ qds)	0.3 % ofloxacin otic solution (Floxin®) 5 drops once daily versus Cortisporin® (polymyxin B 10,000 U/ml; neomycin sulphate 3.5 mg/ml; hydrocortisone 10.0 mg/ml) 3 drops 4 times daily Dose: see above	7 to 10 days	Not specified (presumably not performed as this is a paediatric study)	Concurrent medication: no systemic or topical antibiotics, steroids or non-steroidal anti-inflammatory drugs in the preceding 7 days. No over-the-counter therapy in the preceding 36 hours. No medications were permitted during the study except at the discretion of the investigator (e.g. topical acne medication or chronic pain medications, including steroidal and non-steroidal ant-inflammatory drugs, with no change in dose during the entire study were permitted)
Slack 1987	Acidifying agent versus antibiotic/steroid versus	Boric acid 4% (with absolute alcohol 25% + sterile water to 100%) versus Otosporin® (polymyxin B sulphate 10,000 units/ml; neomycin sulphate 0.5%; hydrocortisone 1%) versus	Until cure	All groups: performed at initial visit and weekly thereafter	Concurrent medication: not reported

Table 4. Intervention regimens used *(Continued)*

	antibiotic/antifungal/steroid	polymyxin B sulphate 15,000 units/ml + flucinolone acetonide 0.1% + econazole 1% + methanol 5% + glycerol 10% + polyethylene glycol '300' to 100% Dose: 2 drops 4 times daily			
Tsikoudas 2002	Antibiotic/steroid versus steroid-only version	Vista-Methasone N® (steroid + neomycin sulphate 0.5%) versus Vista-Methasone® (steroid) Dose: not stated	14 days	All groups: performed at initial visit	Concurrent medication: not reported
van Balen 2003	Acidifying agent versus acidifying agent/steroid versus antibiotic/steroid	Acetic acid versus acetic acid + steroid (0.1% triamcinolone acetonide) versus steroid + antibiotic (0.66 mg dexamethasone phosphate sodium; 5 mg neomycin sulphate; 10,000 IU polymyxin B sulphate per ml) Dose: 3 drops 3 times daily	Up to 21 days	All groups: performed on initial visit. Wick inserted for 24 hours if ear canal was swollen and repeated as necessary.	Concurrent medication: not reported
Wadsten 1985	Antibiotic/steroid versus antibiotic/steroid	Sofradex® (framycetin, gramicidin, dexamethasone) versus Terra-Cortril® with polymyxin B (TPB) (oxytetracycline, polymyxin B, hydrocortisone) Dose: 3 to 5 ear drops 3 to 4 times daily	7 days	All groups: performed on initial visit. Wick inserted for 24 hours if ear canal was swollen.	Concurrent medication: oral salicylates and indomethacin were given to those experiencing acute pain and tenderness

bd = twice a day
NQ = non-quinolone
od = once a day
Q = quinolone
qds = four times a day
tds = three times a day

Table 5. Outcomes assessed

Study ID	Clinical			Microbial			Safety	Other outcomes
		Assessment method and time	Measurement scale/ severity grading		Assessment method and time	Measurement scale/ severity grading		
Cannon 1967	Clinical response	Clinical examination by one physician on day 5 and 10	Response graded as good, fair, none, worse	—	—	—	—	—
Emgard 1999	1. Resolution of clinical signs 2. Resolution of symptoms	1. Clinical exam day 0, 3, 7, 11, 21 2. Visual analogue scale: 0 to 100 mm	1. Scoring system and parameters assessed: swelling of EAC (0 = none, 1 = mild with annulus visible in 2 of 4 quadrants, 2 = moderate with annulus not visible in any quadrant, 3 = severe with an occluded EAC) Extension of redness outside EAC onto the pinna (0 = none, 1 = extends to tragus and meatus, 2 = extends to cavis auris, 3 = extends to mastoid process) Effusion of the EAC (0 = dry, 1 = moist, 2 = fluid present and suction needed, 3 = otorrhoea) Colour of the EAC (0 = pale, 1 = pink, 2 = red, 3 = purple) 2. Visual analogue scale: 0 to 100 mm; parameters assessed: pain, itching, ability to work, ability to sleep	—	—	—	—	—

Table 5. Outcomes assessed *(Continued)*

Freedman 1978	1. Mean symptom score 2. Mean change in symptoms severity scores between visits	1. and 2. rated on days 1, 3, 7, and day 21	Parameters rated: redness, oedema, weeping, scaling, pain, itching Scores: 0 = clear, 1 = mild involvement, 2 = moderate involvement, 3 = marked involvement	Effectiveness against pathogens	Swabs taken on day 1, 7 and 21	Comparison of the number of cultures for individual organism pre and post-therapy made	—	—
Johnston 2006	1. Clinical resolution	Otoscopy at 0, 2 and 4 weeks	Nil mentioned	—	—	—	—	—
Jones 1997	1. Clinical response 2. Clinical-microbiological response 3. Mean scores for tenderness and secretion/exudates pre-and post-therapy 4. Satisfaction with the treatment received	1. Investigator assessment at test-of-cure visit 2. Investigator assessment and bacteriologic efficacy response at test-of-cure visit	1. Outcome deemed as either: sustained clinical cure, subsequent clinical cure, clinical failure, clinical relapse, or indeterminate 2. See above for clinical responses available and see across for microbial responses available 3. This is based on: measurement of the EAC diameter on each visit using speculums Use of the severity scale, scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe; for the following parameters: oedema, tenderness, erythema, and secretion/exudates 4. Satisfaction classed as: 1 = extremely satisfied, 2 = very satisfied, 3 = moderately satisfied, 4 = satisfied, 5 = not satisfied, 6 =	1. Microbial response	1. Bacteriologic efficacy response at test-of-cure visit	1. Outcome deemed as either: documented eradication, presumed eradication, persistence, recurrence, superinfection, reinfection, colonisation, or not evaluable	—	—

Table 5. Outcomes assessed *(Continued)*

			moderately dissatisfied, 7 = very dissatisfied					
Masood 2008	1. Pain score 2. Clinical sign score	1. Day 0 and 2 2. Day 0 and 2	1. VAS from 0 to 10 2. Sign score: Ear canal swelling: nil = 0, < 50% = 1, > 50% = 2 Tenderness: nil = 0, present = 1 Erythema: nil = 0, present = 1	_	_	_	_	_
Mosges 2007	1. Clinical symptom score reduction 2. Subscore mean reduction 3. Pain score (VAS) reduction 4. Paracetamol consumption 5. Efficacy/tolerability rating (by patient and investigator)	1. Days 0, 3 to 5, 9 to 11 2. Days 0, 3 to 5, 9 to 11 3. Days 0, 3 to 5, 9 to 11 4. Day 9 to 11 5. Day 9 to 11	1. and 2. redness, swelling, pain and secretion, each rated on a 4-point scale 0 = none, 1 = mild, 2 = moderate, 3 = severe 3. 100 mm visual analogue scale (VAS) 4. Number of tablets consumed was noted 5. Rated as either very good, good, satisfactory or poor	Baseline cultures were taken to provide ensure bacteriological profiles across groups were similar	Day 0	_	_	_
Mosges 2008	1. Change in Clinical Symptom Score (CSS) 2. Change in individual subscore 3. Change in pain score (VAS) 4. Paracetamol consumption	1. From baseline to visit 2, and baseline to visit 3 2. From baseline to visit 2, and baseline to visit 3 3. From baseline to visit 2, and baseline to visit 3 4. From visit 1 to visit 3 5. At visit 3 6. At visit 3	1. CSS = 0 to 12 (redness (0 to 3), swelling (0 to 3), pain (0 to 3), secretion (0 to 3)) 2. Redness (0 to 3), swelling (0 to 3), pain (0 to 3), secretion (0 to 3) 3. VAS scale (no further detail given) 4. Tablet consumption	_	_	_	_	_

Table 5. Outcomes assessed *(Continued)*

	5. Patients global assessment of efficacy 6. Complete clinical cure (CSS = 0)		5. Very good, good, satisfactory, poor 6. CSS = 0					
Neher 2004	1. Time to healing/complete disappearance of inflammation 2. Intensity of pain	1. Daily clinical examination 2. Measured using a visual analogue scale (0 to 10) before every application procedure	1. 6-point scale: 0 = outer ear canal without signs of inflammation, to 5 = serious inflammation with ear canal completely obstructed by swelling) The time in days required until complete healing (score 0) 2. Visual analogue scale: 0 = no pain, 10 = intolerable pain	—	—	—	—	—
Olivera 2004	Resolution of symptoms	Physician assessment at entry, visit 2 (48 to 72 hours later), and visit 3 (7 days later)	Parameters and their grading: drainage (purulent, mucous, none); swelling (intense, moderate, slight, none); pain (existent, non-existent); redness (existent, non-existent)	—	—	—	—	—
Roland 2004	1. Clinical resolution 2. Investigator assessment	1. Clinical exam at day 18 (test-of-cure day) 2. Clinical exam at each study visit	1. Scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe Parameters assessed: signs and symptoms of acute otitis externa including inflammation, oedema, tenderness and otic discharge 2. Outcomes rated as either: cured = 0, improved = 1, unchanged = 2, or worsened = 3	Microbiological eradication	Ear swabs taken at day 1 and day 18 (test-of-cure day);	Outcome rated as either: success (= eradication = culture negative), failure, or re-infection	—	—

Table 5. Outcomes assessed *(Continued)*

Roland 2007	1. Patient reported pain 2. Investigator assessment 3. Analgesic use	1. Twice daily patient ear pain diary 2. Clinical exam days 3, 8, 18 3. Twice daily patient analgesic use diary	1. Pain scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe 2. Inflammation (moderate, severe); oedema (mild, moderate, severe); tenderness (yes, no); discharge (present, not present) 3. Unclear; patients split into no analgesic use, non-narcotic analgesics or narcotic analgesic use	—	—	—	—	—
Roland 2008	1. Clinical-microbiological response 2. Time to end of ear pain 3. Investigator assessment of tenderness and otalgia	1. Investigator assessment at end-of-therapy (EOT) AND test-of-cure visit (TOC), AND microbial assessment at EOT OR TOC visit N.B. visit number: #1 = at entry (day 1) #2 = day 3 to 5 #3 = EOT (day 8 Cipro/HC, day 11 NPH + Amox) #4 = TOC (day 14 to 17 Cipro/HC, day 17 to 20 NPH + Amox) 2. Daily patient diaries 3. Investigator assessment at visit 2, 3 and 4	1. Response to therapy = improved or cured at EOT AND cured at TOC, AND presumed or confirmed microbial eradication at EOT or TOC visit No response = if above criteria not met 2. 0 = none, 1 = mild, 2 = moderate, 3 = severe 3. 0 = cured, 1 = improved, 2 = no change, 3 = worse	1. Clinical-microbiological response (see previous columns for further details) 2. Microbiologic eradication (percentage of patients with resolution of disease-specific infection present at visit 1)	1. Investigator assessment at end-of-therapy (EOT) AND test-of-cure visit (TOC) , AND microbial assessment at EOT OR TOC visit 2. Visit 1, EOT, TOC	1. (See clinical columns) 2. Categorised as either eradication, reinfection/superinfection, or failure	—	—
Sabater 1996	Clinical cure	Clinical exam at day 8	Evaluation of otorrhoea, otalgia, and otoscopic signs	—	—	—	—	—

Table 5. Outcomes assessed *(Continued)*

Schwartz 2006	1. Clinical response 2. Clinical-microbiological response in microbiologically evaluable patients 3.Pain 4. Adverse events	1. Assessed with reference to baseline evaluations: investigator determined overall clinical response at end-of-therapy visit and test-of-cure visit Sponsor determined/assigned overall clinical response at test-of-cure visit 2. Ear swabs taken at pre-therapy visit and at end-of-therapy and/or test-of-cure visit 3. Patient/guardian diaries; during the days of treatment 4. Patient/guardian diaries; recorded on a daily basis	1. Investigator determined overall clinical response at: End-of-therapy visit: assigned clinical cure, clinical improvement, clinical failure, or indeterminate Test-of-cure visit: assigned sustained clinical cure or subsequent clinical cure (either classed as a clinical cure) or clinical failure Sponsor determined/assigned overall clinical response at test-of-cure visit; cure = complete resolution of signs and symptoms with the exception of mild erythema, tenderness, oedema; failure = all other responses 2. Clinical-microbiological outcome rated as cure or failure	1. Clinical-microbiological response (see previous columns for further details) 2. Microbiologic response	1. and 2. Ear swabs taken at pre-therapy visit and at end-of-therapy and/or test-of-cure visit	1. (See previous columns) 2. Outcomes rated as either: eradication, persistence, or recurrence	—	—
Slack 1987	Clinical cure	Signs and symptoms assessed on a weekly basis	Parameters and scores: itching, pain, burning, deafness, discharge; scale of 0 to 3 used for each symptom Erythema, swelling, debris, presence of pus; scale of 0 to 3 used for each sign Giving a total severity score out of 27 However, cure was not defined	—	—	—	—	—

Table 5. Outcomes assessed *(Continued)*

Tsikoudas 2002	1. Signs score 2. Symptoms score	1. Investigator assessment of degree of debris and canal oedema on day 0, 3, 7, 11 2. Patients report of blockage, pain, discharge and itching on day 0, 3, 7, 11	1. 10 cm linear analogue assessment sheet; parameters: debris and canal oedema; results are therefore out of 202. 10 cm linear analogue assessment sheet; results for the 4 parameters is therefore out of 40	—	—	—	—	—
van Balen 2003	1. Time to recovery 2. Cure rate 3. Recurrence	1. Patient diary; day 0 to 21 2. Clinical exam at day 7, 14, 21 3. Telephone call to patient at day 42	1. Recorded extent of pain, itchiness, otorrhoea, hearing loss, stuffy feeling, side effects and compliance with treatment 2. Clinical assessment: to determine if the patient had recovered (no further details provided) and check compliance from the amount of drug remaining 3. Patients asked if their symptoms had recurred	—	—	—	—	—
Wadsten 1985	Clinical resolution	Clinical examination at day 14	Outcomes rated as either: cured or not cured (no further details provided)	—	—	—	—	—

Amox = amoxicillin
Cipro/HC = ciprofloxacin + hydrocortisone
EAC = external auditory canal (the ear canal)
EOT = end-of-therapy
NPH = neomycin + polymyxin B + hydrocortisone
TM = tympanic membrane
TOC = test-of-cure

Table 6. Safety

Study ID	Treatment	Allergic reactions	Ototoxicity	Other adverse events
Cannon 1967	Methylprednisolone disodium phosphate (1.33 mg/ml) and neomycin sulphate (5 mg/ml) + 'vehicle' versus the 'vehicle'. The 'vehicle' comprised sodium citrate, sodium chloride, polysorbate 80, sodium bisulphite, phenethyl alcohol, benzalkonium chloride and sodium hydroxide. Dose: 4 drops 3 times daily	—	—	Nil mentioned
Emgard 1999	0.5% betamethasone dipropionate (Diprosone®) + loratadine 20 mg od 10/7 versus 0.5% betamethasone dipropionate + oral placebo (no further details provided about this) Dose: ear drops 4 drops 4 times daily for the first week, 4 drops once daily from day 8 to 11	—	—	No side effects were reported
Freedman 1978	Coly-Mycin S® (each ml contains colistin sulphate 3 mg + neomycin sulphate 3.3 mg + hydrocortisone acetate 10 mg (1%); thonzonium bromide 0.5 mg (0.05%), polysorbate '80', acetic acid and sodium acetate in a buffered vehicle; thimerosal 0.002% added as a preservative) versus placebo (a starch solution with a turbidity matching that of the antibiotic drop) Dose: 4 drops 3 times daily	—	—	Nil mentioned
Johnston 2006	2% glacial acetic acid (EarCalm®) versus 2% glacial acetic acid, 0.1% dexamethasone and 3250 U/ml neomycin sulphate (Otomize®) Dose: 1 puff 3 times a day	—	—	Nil mentioned
Jones 1997	Ofloxacin 0.3% 10 drops twice daily adults, 5 drops twice daily children versus Cortisporin® (neomycin + polymyxin B + hydrocortisone) 4 drops 4 times daily adults, 3 drops 4 times daily children Dose: see above	—	—	Treatment related adverse events were more commonly reported in adults, but no differences were noted between treatment groups Ofloxacin versus Cortisporin® (adults): Pruritis: 6.3% versus 3.8% Erythematous rash: 0.6% versus 0.6% Application site reaction: 3.8% versus 3.8% Dizziness: 0.6% versus 1.3% Vertigo: 1.3% versus 1.9% Earache: 2.8% versus 3.5%

Table 6. Safety *(Continued)*

				(Children): Application site reaction: 0% versus 2.1% Eczema: 0.7% versus 0% Follicular rash: 0.7% versus 0% Pruritis: 0% versus 0.7% Dizziness: 0.7% versus 0% Earache: 0.7% versus 0.7% Taste perversion: 0% versus 0.7% Dizziness or vertigo may have occurred as a result of putting cold drops in the ear
Masood 2008	10% glycerine-ichthammol (GI) solution on ribbon gauze versus Triadcortyl® ointment on ribbon gauze (triamcinolone acetonide 0.1%, gramicidin 0.025%, neomycin sulphate 0.25%, nystatin 100,000 units/g) Dose: medicated dressing inserted into ear canal for 48 hours	—	—	Nil reported or observed
Mosges 2007	Polymyxin B sulfate (7500 IE/g) + bacitracin (300 IE/g) + hydrocortisone acetate (10 mg/g) ointment (Polyspectran HC® Salbe) versus polymyxin B sulfate (7500 IE/g) + bacitracin (300 IE/g) ointment	1 adverse event was rated as an adverse drug reaction: this was a mild sudden hearing loss that occurred in 1 patient in the antibiotic only group. This was transient and resolved spontaneously on the same day.	—	Antibiotic with steroid: 13 adverse events (4 ear and labyrinth disorders, 1 eye disorder, 8 infections and infestations, 1 respiratory, thoracic and mediastinal disorder) Antibiotic only: 18 adverse events (2 ear and labyrinth disorders, 1 eye disorder, 1 gastrointestinal disorder, 1 general disorder and administration site condition, 5 infections and infestations, 7 nervous system disorders, 1 respiratory, thoracic and mediastinal disorder)
Mosges 2008	Polymyxin B sulfate 7500 IU + neomycin sulfate 3500 IU versus dexamethasone sodium phosphate 0.132% + polymyxin B sulfate 7500 IU + neomycin sulfate 3500 IU Dose: 2 drops 3 times daily	—	—	13 adverse events (10 antibiotic, 3 antibiotic/steroid) 11 patients (10 antibiotic, 1 antibiotic/steroid); i.e. the 1 antibiotic/steroid patient who suffered an adverse event had 3 But only 4 adverse events definitely related to study medication; all in antibiotic group; 1 short-lived otalgia, and 3 itching
Neher 2004	2 ml 1% NCT (N-chlorotaurine) once daily versus 1 ml Otosporin®	No allergic or irri-	—	Nil mentioned

Table 6. Safety *(Continued)*

	(1.27 mg polymyxin B sulphate + 5 mg neomycin sulphate + 10 mg hydrocortisone per ml) once daily Dose: see above	tative effects were observed		
Olivera 2004	0.3% ciprofloxacin glycerin solution versus 0.3% ciprofloxacin aqueous solution Dose: 3 drops twice daily	—	—	None reported during the study period 1 patient in each group reported pruritis after the end of the treatment period
Roland 2004	Ciprodex® (0.3% ciprofloxacin + 0.1% dexamethasone) (3 drops twice daily for children, 4 drops twice daily for 12 years and over) versus Cortisporin® (neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1.0%) (3 drops 3 times daily for children, 4 drops 3 times daily for 12 years and over) Dose: see above	—	—	Adverse events reported during the study were generally mild to moderate and usually resolved with or without treatment Ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone: Otic adverse events: Pruritis: 3 versus 9 Superinfection/pain: 2 (discontinued from study and given other treatment) versus 2 Discomfort: 0 versus 3 Decreased hearing: 0 versus 2 Non-otic adverse events: Paraesthesia: 1 versus 0 Erythema: 0 versus 1; both of these adverse events were mild and resolved without treatment
Roland 2007	Ciprofloxacin 0.3% + dexamethasone 0.1% (3 drops twice daily (adults); 4 drops twice daily (children)) versus neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1.0% (3 drops 3 times daily (adults); 4 drops 3 times daily (children)) Dose: see above	—	—	No patients in either treatment group discontinued the study because of treatment-related adverse events
Roland 2008	Ciprofloxacin 0.2% + hydrocortisone 1% (3 drops 2 times daily x 7 days) versus neomycin 0.35% + polymyxin B 10,000 IU/ml + hydrocortisone 1% (adults: 4 drops 3 times daily + up to 500 mg amoxicillin 3 times daily for 10 days; children: 3 drops 3 times daily + 40 mg/kg/day in 3 divided doses for 10 days) Dose: see above	—	—	No deaths or serious treatment related adverse events were reported for either treatment group. Only 1 patient discontinued the study because of a treatment related adverse event (from the neomycin/polymyxin/hydrocortisone + amoxicillin group)
Sabater 1996	0.5% ciprofloxacin versus 0.3% gentamicin Dose: 5 drops 3 times daily	—	—	No notable side effects encountered for either drug
Schwartz 2006	0.3 % ofloxacin otic solution (Floxin®) 5 drops once daily versus Cor-	Application site	—	Safety evaluation performed in 277 paediatric patients. Treatment-related adverse events similar in

Table 6. Safety *(Continued)*

	tisporin® (polymyxin B 10,000 U/ml; neomycin sulphate 3.5 mg/ml; hydrocortisone 10.0 mg/ml) 3 drops 4 times daily Dose: see above	reaction: ofloxacin 22.3%; neomycin/polymyxin 20.3%		both arms and were mild to moderate in severity (application site reactions, diarrhoea, otitis media, ear ache, coughing). No deaths or serious adverse events were reported during the study. No side effects necessitated discontinuation of therapy.
Slack 1987	Boric acid 4% (with absolute alcohol 25% + sterile water to 100%) versus Otosporin® (polymyxin B sulphate 10,000 units/ml; neomycin sulphate 0.5%; hydrocortisone 1%) versus polymyxin B sulphate 15,000 units/ml + flucinolone acetonide 0.1% + econazole 1% + methanol 5% + glycerol 10% + polyethylene glycol '300' to 100% Dose: 2 drops 4 times daily	—	—	8 patients complained of stinging; 4 in the boric acid group and 4 in the polymyxin B/fluocinolone acetonide/econazole group; only 1 in the boric acid group had to discontinue treatment
Tsikoudas 2002	Vista-Methasone N® (steroid + neomycin sulphate 0.5%) versus Vista-Methasone® (steroid) Dose: not stated	—	—	Nil mentioned
van Balen 2003	Acetic acid versus acetic acid + steroid (0.1% triamcinolone acetonide) versus steroid + antibiotic (0.66 mg dexamethasone phosphate sodium; 5 mg neomycin sulphate; 10,000 IU polymyxin B sulphate per ml) Dose: 3 drops 3 times daily	—	—	158 patients (74%) mentioned side effects at least once. 3 patients discontinued treatment because of side effects (2 in acetic acid group and 1 in the steroid and acetic acid group). Although the acetic acid group did have more severe burning, pain, or irritation than the other two groups, no significant differences were found between treatment groups.
Wadsten 1985	Sofradex® (framycetin, gramicidin, dexamethasone) versus Terra-Cortril® with polymyxin B (TPB) (oxytetracycline, polymyxin B, hydrocortisone) Dose: 3 to 5 ear drops 3 to 4 times daily	—	—	Nil mentioned

bd = twice a day
BD = betamethasone dipropionate
HCPB = hydrocortisone acetate + oxytetracycline + polymyxin B
od = once a day
tds = three times a day
TMJ = temporo-mandibular joint

Table 7. Topical antiseptic versus antiseptic/steroid versus antibiotic/steroid

Review: Interventions for acute otitis externa
Comparison: Topical antiseptic versus antiseptic/steroid versus antibiotic/steroid

Table 7. Topical antiseptic versus antiseptic/steroid versus antibiotic/steroid *(Continued)*

Outcome: Time to recovery	Median duration to recovery (days)	95% confidence interval (days)
Study: van Balen 2003		
Acetic acid	8.0	7.0 - 9.0
Acetic acid + steroid	7.0	5.8 - 8.3
Antibiotic + steroid	6.0	5.1 - 6.9

Table 8. Topical quinolone antibiotic versus non-quinolone/steroid

Review: Interventions for acute otitis externa		
Comparison: Topical quinolone antibiotic versus non-quinolone/steroid		
Outcome: Mean daily pain scores in ITT patients		
Study: Schwartz 2006	Quinolone antibiotic	Non-quinolone/steroid
Day 1	4.8 (+/-2.52)	4.6 (+/-2.52)
Day 3	2.0 (+/-2.15)	2.0 (+/-2.07)

Table 9. Topical antibiotic/steroid versus antibiotic only version

Review: Interventions for acute otitis externa			
Comparison: Antibiotic/steroid versus antibiotic only version			
Study: Mosges 2008			
Outcome: Clinical symptom score			
	Antibiotic/steroid	Antibiotic	P value
Mean change from baseline (day 1) to visit 2 (day 3 to 5)	4.0+/-2.2	3.6+/-2.0	Not significant
Mean change from baseline (day 1) to visit 3 (day 8 to 12)	6.4+/-2.2	6.0+/-2.7	Not significant

Table 10. Topical antibiotic/steroid versus steroid-only version

Review: Interventions for acute otitis externa
Comparison: Topical antibiotic/steroid versus steroid-only version

Table 10. Topical antibiotic/steroid versus steroid-only version *(Continued)*

Outcome: Null hypothesis (addition of aminoglycoside makes no difference to patient outcome) at day 11		
Study: Tsikoudas 2002 (Mann-Whitney U-test)		
Patient assessment scores	No significant differences between the 2 groups	P = 0.30
Observer assessment scores	No significant differences between the 2 groups	P = 0.164

Table 11. Topical antibiotic/steroid versus antibiotic only version

Review: Interventions for acute otitis externa			
Comparison: Antibiotic/steroid versus antibiotic only version			
Study: Mosges 2007			
Outcome: Clinical symptom score			
	Antibiotic/steroid (N = 77)	Antibiotic (N = 72)	P value
Change from baseline to visit 2 (day 3 to 5)	-3.48 +/- 2.49	-3.36 +/- 2.12	0.3514
Change from baseline to visit 3 (day 9 to 11)	-6.52 +/- 3.10	-5.92 +/- 2.92	0.1440

Table 12. Antibiotic/steroid/anti-fungal dressing versus antiseptic/astringent dressing

Review: Interventions for acute otitis externa			
Comparison: Antibiotic/steroid/antifungal dressing versus antiseptic/astringent dressing			
Study: Masood 2008			
Outcome: Pain and signs score improvement			
	Antiseptic/astringent group (N = 32)	Antibiotic/steroid/antifungal group (N = 32)	P value
Mean pain improvement (range)	3.90 (1 to 7)	5.25 (1 to 8)	P < 0.001
Mean signs score improvement (range)	2.06 (1 to 4)	2.25 (1 to 4)	P = 0.979

Table 13. Oral antibiotic + topical (non-quinolone) antibiotic/steroid drop versus topical (quinolone) antibiotic/steroid drop

Review: Interventions for otitis externa

Table 13. Oral antibiotic + topical (non-quinolone) antibiotic/steroid drop versus topical (quinolone) antibiotic/steroid drop *(Continued)*

Comparison: Oral antibiotic + topical (non-quinolone)antibiotic/steroid drop versus topical (quinolone)antibiotic/steroid drop

Study: Roland 2008

Outcome:

		Oral antibiotic + topical (non-quinolone) antibiotic/steroid drop	Topical (quinolone) antibiotic/steroid drop	P value	95% CI
Response	Yes	53	66		
	No	6	4	0.5109	-4.98 to 13.89
Microbial eradication		53	67	0.4086	-3.60 to 11.84
Mean time to end of ear pain (days)		6.68	6.45	0.9644	

APPENDICES

Appendix 1. Search strategies

PubMed	EMBASE (Ovid)	CINAHL (EBSCO)	CENTRAL
#1 "OtitisExterna"[Mesh] #2 "Otitis"[Mesh] #3 (otitis [tiab] OR inflamm* [tiab] OR infect* [tiab]) #4 "Ear, External"[Mesh] #5 (ear [tiab] OR "auditory canal" [tiab]) AND externa* [tiab]) #6 pinna [tiab] #7 (#2 OR #3) AND (#4 OR #5 OR #6) #8 ((swimmer* [tiab] OR tank [tiab] OR "hot weather" [tiab] OR tropical [tiab]) AND ear* [tiab]) #9 #1 OR #7 OR #8	1 External Otitis/ 2 exp Otitis/ 3 (otitis or inflamm* or infect*).tw. 4 3 or 2 5 exp *External Ear/ 6 ((ear or "auditory canal") and externa*).tw 7 pinna.tw. 8 6 or 7 or 5 9 8 and 4 10 ("swimmer* ear" or "tropical ear" or "hot weather ear" or "tank ear").tw 11 1 or 10 or 9	S1 (MH "Otitis Externa") S2 (MH "Otitis+" S3 TX (otitis OR inflamm* OR infect* S4 (S2 OR S3) S5 (MH "Ear, External+" S6 TX (ear AND externa* S7 TX pinna S8 (S5 OR S6 OR S7) S9 (S4 AND S8) S10 TX ("swimmer* ear" OR "tropical ear" OR	#1 OTITIS EXTERNA #2 OTITIS #3 otitis #4 inflamm* #5 infect* #6 #2 or #3 or #4 or #5 #7 EAR, EXTERNAL #8 (extern* near ear) #9 (extern* near auditory next canal) #10 pinna* #11 #7 or #8 or #9 or #10 #12 #6 and #11 #13 swimmer* ear #14 tank ear #15 hot weather ear #16 tropical ear #17 #13 or #14 or #15 or #16 #18 #1 or #12 or #17

(Continued)

		"hot weather ear" OR "tank ear") S11 S1 OR S9 OR S10	
Web of Science	**BIOSIS Previews (Ovid)**	**mRCT**	**CAB Abstracts (Ovid)**
#1 TS=((otitis OR inflamm* OR infect*) AND ((externa* AND ear) OR pinna)) #2 TS=("swimmer* ear" OR "tank ear" OR "hot weather ear" OR "tropical ear") #3 #2 OR #1	1 exp Otitis/ 2 (otitis or inflamm* or infect*).tw 3 2 or 1 4 exp *External Ear/ 5 ((ear or "auditory canal") and externa*).tw 6 pinna.tw. 7 5 or 6 or 4 8 7 and 3 9 ("swimmer* ear" or "tropical ear" or "hot weather ear" or "tank ear").tw 10 8 or 9	otitis AND externa%	1 exp Otitis/ 2 (otitis or inflamm* or infect*).tw 3 2 or 1 4 exp *External Ear/ 5 ((ear or "auditory canal") and externa*).tw 6 pinna.tw. 7 5 or 6 or 4 8 7 and 3 9 ("swimmer* ear" or "tropical ear" or "hot weather ear" or "tank ear").tw 10 8 or 9

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 1, 2010

Date	Event	Description
19 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Vivek Kaushik (lead author): original concept, obtaining the papers, data extraction and writing the early drafts, protocol development, design of search strategy, quality assessment, analysis and interpretation of data, writing of review.

Tass Malik: protocol development, quality assessment, analysis and interpretation of data, writing of review.

Shakeel Saeed: clinical, methodological and editorial input and advice.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [therapeutic use]; Anti-Infective Agents, Local [administration & dosage]; Histamine Antagonists [therapeutic use]; Hygiene; Otitis Externa [microbiology] [prevention & control] [*therapy]; Randomized Controlled Trials as Topic; Steroids [therapeutic use]

MeSH check words

Adult; Child; Humans